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Editorial

THE STETHOSCOPE: A SOURCE OF DIAGNOSTIC AID AND CONCEPTUAL ERRORS IN RHEUMATIC HEART DISEASE

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THE patient who has had rheumatic fever spends the rest of his life under a cardiac cloud. If he has not already acquired overt evidence of heart disease, he must live in fear that he has a small, imperceptible, inflammatory nidus which may eventually develop into a damaged valve.

The concept that all rheumatic patients have either actual or potential heart disease comes from several sets of data: (1) Patients dying of acute rheumatic fever invariably show severe cardiac damage.[1-3] (2) Rheumatic heart disease is frequently found[3,4] clinically, surgically, or pathologically in patients who have no history of rheumatic fever. (3) Many patients who had seemed to escape heart disease after an identified attack of rheumatic fever were eventually found to have evidence of valvular damage in clinical follow-up studies[5-13] performed many years later. The patients who subsequently developed heart disease could not at the beginning be distinguished from those who were going to remain free of it. Therefore, the label of "potential" heart disease has been given to all patients who have no obvious cardiac damage after having rheumatic fever.

Some of the major data discussed here were obtained through the Irvington House Rheumatic Fever Prophylaxis Research Clinic, which is supported in part by grants from the United States Public Health Service, American Heart Association, New York Heart Association, Westchester Heart Association, and Wyeth Laboratories.

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As a result of these features, a strongly cardiopathic orientation has developed toward rheumatic fever. The pathologic data make it seem that rheumatic heart disease is ubiquitous, with or without obvious rheumatic fever, and the clinical data imply that many patients who are spared at first are stricken later. With this orientation, clinicians diligently search the rheumatic patient's auscultatory, roentgenographic, and electrocardiographic data to find in vivo evidence of the lesions which are so often seen post mortem. With this orientation, too, there has come the belief that rheumatic fever is always a chronic disease whose ultimate manifestations may not occur until many years after the acute attack.

The concepts derived from these data have virtually achieved the status of axioms. Like all medical axioms, however, they must undergo periodic critical re-evaluation. When this is done, the possibility arises that two kinds of errors may inadvertently have been allowed to influence the interpretations of the data.

The *pathologic* results may have created an error of *omission*. Pathologists have assiduously examined autopsy material for the deranged anatomic, histologic, and physiologic manifestations of rheumatic heart disease. They have found it where they expected it, i.e., in patients who had rheumatic fever or rheumatic heart disease that was clinically identified. They have also found it where they did not expect it, i.e., in patients whose lesions were unsuspected and undetected in their history and physical examinations. Although several clinical studies[14-16] have shown that certain patients apparently remain free of heart disease after rheumatic fever, the pathologists have not considered this opposite facet of the problem. No studies have been done to determine how often patients with histories of rheumatic fever die *without* having rheumatic heart disease. Because of this investigative void, the pathologists' reports have emphasized the presence of cardiac lesions in rheumatic fever and nothing has been said about their possible absence.

The *clinical* data may have created an error of *commission*. The deductions of the long-term clinical studies used the following reasoning process: At the end of an acute rheumatic attack, the examining physicians noted no significant murmurs in certain patients, who were thereby deemed free of heart disease. When these patients were re-examined many years later, some were found to have significant murmurs. It was concluded that changes had occurred in the patients' hearts, due either to insidious valvular scarring or the recurrence of active rheumatic disease. While this conclusion seems reasonable, there is an alternative explanation which was not ruled out. It is possible that the observed "changes" may sometimes have occurred in the examiner rather than in the patient.

There can be no quarrel with the anatomic data of the pathologists. One can only speculate about the nature and effects of the data they have *not* obtained. The results and interpretations of the clinicians, however, allow more room for skepticism. These data could not be verified by pathologic examination and they depend upon auscultation of the heart, a procedure which is highly subjective and which leaves no permanent record. Because of its ephemeral qualities, auscultation has often been depreciated and deplored as a diagnostic adjunct.

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"Need we continue," wrote a prominent British cardiologist,[17] "slavishly to listen daily to these hearts when auscultation tells us almost nothing?" With the stethoscope abjured, many clinicians have turned to electrocardiograms, x-rays, fluoroscopy, and catheters for more "objective" measurements of cardiac status.

Despite its disadvantages, the stethoscope cannot be so easily dismissed. Unlike most other pathologic cardiac conditions, rheumatic heart disease requires certain auscultatory phenomena for its clinical diagnosis. With appropriate murmurs its presence can be suspected and without these murmurs its diagnosis cannot be made, regardless of the presence or absence of a history of rheumatic fever. Neither the electrocardiograph nor radiologic devices can equal the stethoscope as an instrument for performing a clinical "biopsy" upon the acquired pathologic element which is crucial to rheumatic heart disease—the damaged valve. The stethoscope may in time be replaced by electronic or other new methods for recording and interpreting acoustic cardiac phenomena. For the past, present, and imminent future, however, the stethoscope has been and will remain the most frequently used instrument in clinical cardiology. It was employed in all the existing long-term clinical studies of rheumatic fever and is used in all which are in progress. Although it necessitates subjective interpretation by the user, this subjectivity is often no greater than that required in roentgenographic decisions regarding cardiac size or electrocardiographic measurements of the lengths of P-R or Q-T intervals. The stethoscope itself, like all other laboratory and physical diagnostic agents, has been constantly improved, exposed to critical review, and calibrated. The same cannot be said of its complementary agent, the physician. Of all the diagnostic tests in rheumatic fever, the physician's auscultation has been given the least critical appraisal.

Workers in clinical investigation have used highly scientific methods to eliminate error as they train themselves and their technicians in tasks of the laboratory and as they perfect the function of laboratory equipment. When they leave the laboratory for the ward or clinic, however, they have often assumed without further critical calibration that they or any physician can regularly perform auscultation and interpret the acoustic phenomena accurately. The realization that auscultatory interpretations may be occasionally or frequently controversial has led to the disparagement of the stethoscope as a diagnostic tool. Nevertheless, auscultatory data provided the basis for the concept of real or "potential" heart disease in all patients with rheumatic fever. Within this framework, the results of stethoscopic observations in this disease may be reconsidered.

For years it has been known that certain diastolic murmurs are commonly associated with rheumatic heart disease[10]: (1) the high-pitched diastolic blow at the base or along the left sternal border heard *during* and *after* acute attacks and usually attributed to aortic regurgitation; (2) the presystolic crescendo rumble at the apex, often not heard until many years *after* the acute attack, and attributed to mitral stenosis, and (3) the soft, short, mid-diastolic murmur at the apex, associated with a long apical systolic murmur, usually heard only *during* the acute attack, often difficult to distinguish from a physiologic third

heart sound and frequently attributed to mitral valvulitis. Although informal conversations among physicians will elicit the comment that these diastolic murmurs—in particular, the one of aortic regurgitation—often can be heard only with particularly careful auscultation, there has previously been no known quantitative estimation of the frequency with which they escape detection. Using "blind" auscultatory techniques—where physicians examine rheumatic patients without previous knowledge of the chart or each other's opinions—the author and his colleagues have periodically been subjected to the humbling and enlightening experience of failing to detect an unequivocal diastolic murmur which they had recognized at a previous examination but which they now detect only after its existence is pointed out. A recent survey[18] of rheumatic fever patients who were found to have *diastolic* murmurs on arrival at Irvington House showed that the murmurs had not been previously noted in 9 per cent of the patients who came from teaching hospitals and in 39 per cent of those who came from other sources. In the files of the referring institutions, these patients were listed as not having diastolic murmurs. If the patients were not re-examined at the original source of care until many years later and if the murmurs were then detected for the first time, their discovery would inevitably and erroneously be considered as a new event instead of being correctly designated as a *persistent* residue of the now-remote rheumatic attack.

Every physician who studies rheumatic fever patients can recall isolated or frequent instances in which the patient originally had "nothing" on auscultation and was then later found to have "something." If a physician occasionally "misses" a diastolic murmur, he would have no way of knowing this (unless another physician had concomitantly examined the patient and found it). When he later discovers the murmur, the physician is understandably reluctant to assume that he failed to hear it previously and so he concludes that the heart has changed.

The data cited above show that the "unheard" diastolic murmur phenomenon is a significant and frequent event and obviously it can happen to *all* physicians, regardless of their cardiologic skills. Hurried auscultation in noisy clinic settings can be enough to cause it, although other factors, relating to the examiner, can also be at work. If this "missed murmur" phenomenon should occur in the course of a long-term study, its existence might not be recognized for the reasons noted above. Obviously it must occur from time to time, particularly when the patients are examined only sporadically. The patients in whom this occurs are then considered to have developed heart disease after being originally free of it, when actually their heart disease was present from the beginning but was not detected until much later. In this way there may erroneously arise one component of the "potential heart disease" group.

Could any other *nonpathologic* causes be responsible for the later discovery of rheumatic heart disease where it was previously absent? To consider this, a different auscultatory phenomenon—the innocent systolic murmur—must be considered. With different intensities, pitches, qualities, and precordial locations, these physiologic systolic murmurs have been shown[19,20] to occur in 60 to 96

per cent of all normal children and adolescents, and recent work[21] with special microphonic techniques suggests that they occur in virtually *all* normal people. Could such a physiologic systolic murmur coexist with the arthritis or chorea of rheumatic fever? Certainly. Would it be likely to be louder when the patient has fever or tachycardia? Certainly. From its site of presumed origin in the pulmonary artery and its left-sternal-border location of normal maximum audibility, could it be heard at the apex or even, particularly in thin chests, in the axilla? Certainly. Would the murmur be likely to be "discovered" for the first time as the physician listens to the previously normal patient's heart more closely during the rheumatic attack? Certainly. Would the intensity of the murmur be reduced, as the fever and/or tachycardia subside, regardless of the therapy employed? Certainly. Would most physicians interpret this murmur and its "change" as innocent acoustic events, not caused by a pathologic cardiac condition? Hardly. Because of the cardiopathic orientation to rheumatic fever, most physicians are reluctant to discount these events and will assume that the murmur is organic. Since the modified Jones diagnostic criteria[22] for rheumatic carditis have not specifically defined what is meant by a "change" in murmurs, it is usually assumed that the different intensities of the murmur have been due to carditis. Thus the label of acute heart disease is given to a patient who actually has none and who later remains free of it. This does not affect the results of long-term studies since this group of patients may never show cardiac damage. It affects therapeutic studies in rheumatic fever, however, since a triumph over "carditis" may be falsely ascribed to whatever medication was used to treat it.

A somewhat analogous auscultatory situation, not present during the acute attack, may operate to affect the long-term results. Suppose the rheumatic patient is examined many years later and has only a faint systolic murmur which is audible at the left sternal border and apex, without radiating to the axilla. If the observer did not know that this was a "rheumatic" patient, he would probably call it physiologic rather than organic. In the framework of cardiopathic orientation to rheumatic fever, would the murmur a priori be considered pathologic? If the physician who is remote from a medical center is asked to report his follow-up auscultation of such a patient to a group of academic investigators, is he likely to overemphasize the organic importance of any systolic murmurs which may be present? Is he more likely to do so at a 20-year follow-up examination if he knows that the results of 10-year follow-up studies showed that "heart disease" insidiously develops where it was previously absent? Human nature being what it is, the answer to these three questions is probably yes. In this way, then, certain patients who are found to have "heart disease" at follow-up studies may actually have had nothing more than physiologic systolic murmurs which were given excessive significance and which could not be further checked because the investigating team had to depend upon mailed reports from remote physicians.

Physiologic systolic murmurs need not be the only source of "false positive" diagnoses of heart disease. Clinical and phonocardiographic reports[23,24] have called attention to the frequency with which variations in the first sound of the normal heart may simulate the presystolic murmur of mitral stenosis. In patients

who have these acoustic variations and a history of rheumatic fever, most examiners would tend to regard the ausculatory findings as pathologic unless contrary proof were available. One of the early leaders of American cardiology[25] described the pernicious nature of these phenomena and wrote, "The greatest outcry against the stethoscope has come from those who deplore the fact that the murmur revealed by this instrument so often means nothing pathologic yet is regarded by the injudicious examiner as an indication of disease." If these erroneous diagnoses should occur at follow-up examinations, they could create another component of the "potential" group who, it is falsely believed, have developed heart disease.

One other component remains. Suppose the patient's acute rheumatic attack created valvulitis with significant organic murmurs, which later disappeared as the more acute edema and inflammation subsided. If the patient was examined only at the *end* of the acute attack, he would have had no auscultatory evidence of heart disease. If the previously inflamed valve then began to scar, significant murmurs might again be found at a later date, and another patient would have been reclassified from "no heart disease" to "heart disease." In this situation, the crucial cardiac data would have been missed because the patient's status was recorded *after* rather than *during* the acute attack.

The above conjectures suggest, therefore, that the group of patients with no heart disease who later develop heart disease may actually be divided into four components: those whose persistent diastolic murmurs were initially unrecognized, those whose remotely found physiologic acoustic phenomena were mistakenly regarded as pathologic, those whose pathologic murmurs disappeared by the end of the acute attack but later returned, and those in whom valvular damage eventually appeared without any previous clinical evidence of it. Of these four components only the last one validates the concept that rheumatic heart disease insidiously develops in patients who initially escaped it. The first two components arise only because of auscultatory variations. The heart disease which develops in these two groups of patients is really attributable to the stethoscope, and its "development" would presumably be eliminated if more effective auscultatory techniques could be used to recognize its initial presence in one group and its eventual absence in the other. The third component arises because the patients were classified according to their status *after* the acute attack, rather than *during* it. If the follow-up studies in this group had considered the cardiac phenomena which occurred during the acute attack, the original valvular involvement would have been recognized despite its later disappearance. Its future reappearance would therefore be an anticipated possibility, since the original susceptibility of the patient would have been noted.

It may be inferred that the number of patients with no heart disease who later develop heart disease has been artifactiously increased by three groups who have been included by error. The occurrence of these errors is not surprising, because of certain handicaps under which the existing studies were performed:

(1) The clinical diagnosis of rheumatic fever could not always be uniformly made because the Jones criteria[26] and their modifications[22] had not yet been established. The laboratory diagnostic verification was hampered by the absence

of streptococcal antibody methods[27,28] and the lack of other tests which can differentiate rheumatic fever from other conditions, such as lupus erythematosus and congenital heart disease, which may clinically resemble it.

(2) The patients were classified according to their status at the *end* of the acute attack. They were then re-examined at intervals of a year or more, and occasionally the re-examination could not be performed until many years later. In some cases, it was done by a physician in a remote location with whose auscultatory standards the investigators were unfamiliar. In these circumstances, the investigators did not tabulate valvular involvement *during* the acute attack, would have had difficulty in ascertaining the absence of subclinical rheumatic recurrences which might create heart disease, and would have not been able to determine the precise onset and documentation of auscultatory changes.

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(3) The lack of antimicrobial agents meant that the investigators could not eradicate the streptococci which incited the original rheumatic inflammation and could not prevent recurrences of rheumatic activity. They thus dealt with a follow-up population whose freedom from streptococcal inflammation could not be diagnostically or pharmaceutically assured.

With the elimination of these disadvantages, it would be expected that the possible errors of the previous studies would be avoided and that the incidence of *de novo* rheumatic heart disease would be considerably reduced. These conjectures have now been examined in a new investigation, whose methods and techniques were able to remove many of the handicaps of the older studies. In a special research clinic,[29,30] 359 patients who did not have previous heart disease and whose rheumatic fever attacks fulfilled the modified Jones diagnostic criteria were followed while receiving continuous antimicrobial prophylaxis against rheumatic recurrences. They were examined at monthly intervals by bacteriologic, immunologic, and other techniques which detected streptococcal and rheumatic activity. At the same time, the use of "blind" auscultation by multiple examiners, phonocardiographic correlations, and objective approaches to the interpretation of radiographic and electrocardiographic data helped provide prompt and effective recognition of changes in cardiac status.

For this study,[31] the patients were classified into three groups, according to the auscultatory phenomena which occurred *during* the acute attack. The designation "valvulitis" was given to those who developed any of the diastolic murmurs described above. The designation "probable valvulitis" was used for patients without diastolic murmurs who developed what has been previously described as an organic systolic murmur—long, maximally loud at the apex, and transmitted to the axilla. The term "probable" was applied to the "valvulitis" in this group because the authors believed that even rigorous auscultatory criteria could not always differentiate a pathologic apical systolic murmur from a physiologic one. The term "no valvulitis" was given to a third group of patients who did not fulfill the above specific auscultatory criteria, even though most of the patients in this group had other (physiologic) systolic murmurs and many had other features sometimes loosely associated with "carditis." The data of the acute phases of the rheumatic attacks showed that significant cardiac

enlargement, pericarditis, and congestive heart failure occurred almost exclusively in patients who simultaneously had auscultatory evidence of valvular involvement. Thus, three of the four features cited in the modified Jones clinical criteria for carditis seemed to occur only in the presence of the fourth. By contrast, a prolonged P-R interval appeared in about one-third of the patients in each group regardless of valvular involvement. *The follow-up of these patients, under the almost ideal investigative conditions described above, has now extended for over 5 years. The current data show that heart disease is present in about two-thirds (86/129) of the patients who had "valvulitis" and in one-fourth (13/52) of those with "probable valvulitis." The 178 patients who had "no valvulitis" have all remained free of heart disease.*

This meticulous investigation of rheumatic fever sequelae, performed with clinical and laboratory techniques that minimize the disadvantages of earlier studies, has thus produced results which cogently support the validity of the conjectures cited above. The incidence of *de novo* rheumatic heart disease was not merely reduced. *It did not occur.* New evidence of valvular damage subsequently appeared in patients with no heart disease only if they had auscultatory manifestations of valvular involvement during the acute rheumatic attack. All other patients who began with no heart disease remained free of it. The authors noted one exception in a patient who was not part of their study and whose focal presystolic murmur was probably initially undetected. He was originally classified as exhibiting no valvular involvement. When the murmur was discovered several months later, heart disease had thus "developed." Actually it had most likely been persistent and finally recognized.

These striking results will obviously need further confirmation by greater length of follow-up in the patients under surveillance. If the additional observations support the patterns which have presently emerged, the data will have a series of significant implications:

(1) A prolonged P-R interval and other transitory ECG changes in acute rheumatic fever need not represent histopathology. As phenomena of altered electrical conductivity, they may be due to temporary biochemical factors present in the poststreptococcal inflammatory state.

(2) Other presently unknown biochemical factors of this state may produce tachycardia or an increased vigor of cardiac contraction without producing histologic damage. In afebrile patients, these events would tend to make physiologic systolic murmurs louder, with fluctuating intensities which later become minimal. The loud systolic murmur and its change in intensity may then be mistaken for evidence of valvular involvement.

(3) Because of the uncertainties regarding the pathologic cause of systolic murmurs, it is desirable to insist that they not be used as primary evidence of carditis. The evaluation of treatment in first attacks of acute rheumatic carditis should best be done in patients who have *diastolic* murmurs. If the only evidence of carditis is a systolic murmur or a prolonged P-R interval, the therapeutic agent may be credited with a triumph which belongs to physiology and time alone. If the agent is used "prophylactically" to prevent a diastolic murmur, the statistical likelihood is great that the murmur would have remained absent

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regardless of therapy. This is particularly true, as a recent study[32] showed, when no diastolic murmur has appeared within 2 weeks of the onset of symptoms.

(4) Because these stethoscopic observations are so important in predicting cardiac prognosis, the aid of competent clinical consultants as a diagnostic test to confirm the auscultatory phenomena of the acute rheumatic attack is as useful and necessary as roentgenograms, electrocardiograms, and laboratory data. The consultant's auscultation may contribute recognition of a previously unheard diastolic murmur or an injunction against ascribing a physiologic systolic murmur to organic causes.

(5) Physicians can now give the label of "no heart disease" to patients *who have not had valvular involvement* and can remove the stigma and indefinite implications of the "potential" designation from them. In these patients, rheumatic fever is not a chronic disease but an acute poststreptococcal arthritis and/or chorea which subsides without residual cardiac effects. They may be permitted to lead normal lives, free of fears or restraints and subject only to the use of prophylactic medication to prevent rheumatic recurrences.

(6) Although the present results indicate a need for revision of some of the concepts derived from earlier studies, they in no way detract from the admirable quality of these investigations, performed under difficult circumstances and with remarkable diligence. In major part, the present results agree with most of the conclusions of the previous studies. These conclusions, which have been obscured by the cardiopathic aura engendered by the "potential heart disease" concept, were that a majority of patients with rheumatic fever were able to lead useful lives and did not have major cardiac difficulties even when heart disease had persisted or developed. The present data have augmented the earlier conclusions by pointing out the rarity of patients in whom heart disease "develops."

(7) One major group of patients with rheumatic heart disease could not be included in the present or previous studies. These individuals presumably had carditis alone as the sole manifestation of their acute "rheumatic" attack, and did not develop arthritis, chorea, or congestive failure. In the absence of clinical features which would bring them to medical attention, their initial attack could not be recognized. They then appear many years later with rheumatic heart disease but with no history of rheumatic fever. Since their original attacks were unidentified, they cannot be included in any follow-up studies. They constitute a large component of patients who have rheumatic heart lesions and indicate the frequently insidious nature of the disease.

(8) It should be emphasized that the present results and the conclusions derived from them do not in any way minimize the importance and significance of rheumatic fever as a major cause of heart disease. It creates crippling cardiac effects in many patients with obvious attacks and in many, as noted above, whose rheumatic attacks were not identified. The present concepts indicate, however, that the disease has a spectrum and that one side of this spectrum is cardiologically benign. Patients in this part of the spectrum can be identified and reassured. Patients whose disease creates valvular damage remain susceptible to the dangers and complications which these effects may produce.

The stethoscope thus achieves renewed importance as a diagnostic tool in modern medicine. On the basis of inadvertently erroneous auscultatory observations, there has come the concept of "potential heart disease" concerning *all* rheumatic fever patients who do not appear to have it initially. On the basis of newer data, obtained with clinical and laboratory facilities which were hitherto unavailable, the concept may now be revised. The importance of the stethoscope is limited. In patients who have valvular damage, it cannot always indicate the anatomic lesion and it has no utility in determining the degree of pathophysiologic difficulty or the patient's functional capacities and therapeutic needs. Once it has shown the presence of valvular involvement, the stethoscope loses most of its value. For making the crucial distinction regarding the presence or absence of valvular involvement, however, the stethoscope is convenient, portable, inexpensive, and indispensable.

In order to obtain accurate results, the stethoscope *and its user*, like all other diagnostic instruments, must be frequently checked and calibrated. Since it can help diagnose, predict, and create features of rheumatic heart disease, the stethoscope deserves respectful attention from the physician, who is an integral part of its function and whose cultivated skill determines its total effectiveness.

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A CRITICAL REVIEW OF SOME PUBLISHED EXPERIMENTS WITH CHLORPROMAZINE IN SCHIZOPHRENIC, NEUROTIC, AND NORMAL HUMANS

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THERE are many opinions and few facts concerning the action of the various tranquilizers upon the behavior of schizophrenic patients. This review represents an attempt to summarize and evaluate the data concerning one tranquilizer—chlorpromazine—according to certain criteria of scientific investigation.

Our primary interest is in the psychiatric and psychologic behavior of adult schizophrenic patients. Our conceptualization of schizophrenia as the end point of processes which occur universally, however, has led to the inclusion of studies which utilize subjects along a continuum of adjustment. Thus, this is a review of studies which examine the effect of chlorpromazine upon psychologic and psychiatric behavior of adult schizophrenic, neurotic, and normal persons.

The article is divided into three sections. The first section (Review of the Literature) presents the criteria for inclusion in this review and summarizes the resulting data. This section is in the nature of a summary rather than an itemized analysis, since the individual analyses are presented in the Appendix. The second section (Implicit Methodologic Factors) attempts to render explicit certain practices which remain implicit in chemotherapy research and to determine if the data of the first section are related to these practices. The third section (Discussion) attempts to evaluate critically the research process in chemotherapy investigations and to indicate desirable avenues of research

REVIEW OF THE LITERATURE

In order for a study to be included in this section, four criteria had to be satisfied. The first criterion involves the use of a "pure unknown." Studies which

A great debt must be expressed to my wife, Dr. Judith Heilizer, for her help in organizing and writing this article.

utilized chlorpromazine in combination with one or more additional medications were excluded by this criterion. The second criterion involves the concurrent comparison of chlorpromazine and placebo. Studies which did not use a placebo, studies which only used a placebo prior to chlorpromazine administration, and studies which utilized separate chlorpromazine and placebo groups at different times were excluded by this criterion. The third criterion involves the random assignment of subjects to each of the medication groups. Studies which assigned subjects from one ward to one medication group and subjects from another ward to a different medication group were excluded by this criterion. The fourth criterion involves the evaluation of the drug effect separately from the withdrawal effect. Studies which confounded the evaluation of the drug effect with the evaluation of the withdrawal effect (e.g., a Latin Square design with chronic medication) were excluded by this criterion. The single exception was a study by Raymond and coauthors[37] which utilized a partial sequence control. Studies utilizing a Latin Square design with acute medication were not considered to be affected by this criterion.

Some of the data in this section represent the author's computations from data presented in the studies under review. This occurred when: there was no statistical evaluation[3,8,9,19,20,35]; there appeared to be an error in the computations[5]; a more appropriate analysis of the data presented was available[1,10,11]; the data were evaluated by a one-tail test[5,14,22,23,31]; the data were presented for the first stage of a Latin Square design (a study utilizing a Latin Square design was included provided that the data for the first stage were presented and could be analyzed separately)[2,25,39,40]; a chlorpromazine versus placebo comparison was computed from a study which evaluated several drugs versus placebo[2,4,25,27,28,40,45]; additional analyses were performed.[19,20,39]

Throughout this article, two or more experiments utilizing the same subjects or two or more articles describing the same experiment *are treated as a single study*. The 0.05 level by a two-tail test is accepted as statistically significant. Probability values as high as 0.20 are presented for variables which are evaluated by the writer for two reasons: (1) to permit the reader to evaluate the data at a probability level of his own choice and (2) to permit the combination of probability values should an investigator evaluate the same variables with other medications.

PSYCHOTIC SUBJECTS: DRUG EFFECT

The effect of chlorpromazine upon psychotic subjects was investigated in 29 studies. The first consideration is the determination of the generality or specificity of the effect of chlorpromazine upon psychologic behavior. Accordingly, the data are divided into measures of general behavior and measures of specific behavior.

The general measures used fall into two categories: improvement ratings and rating scales. An improvement rating is a relatively unspecified, global statement of change. In principle it may involve ratings of improvement or deterioration on a scale of unlimited range. In practice, it usually involves a three- or

four-point rating from "unchanged" to "very much improved." A rating scale involves judgments of specified behavior in which each rater theoretically evaluates the same behavior regardless of other varying conditions. The rating scales which were used to provide a measure of general change did so by summing across specific items or factors.

Twenty-three of the 29 studies used a measure of general change (Table I). Eleven of these 23 studies used an improvement rating, 7 used a rating scale, and 5 used both an improvement rating and a rating scale. (The general hospital status measure used by Hine[18] was grouped with the improvement ratings, while the psychologic test performance measure used by Gardner and co-workers[9] was grouped with the rating scales.) Eleven of the 18 studies which used either an improvement rating or a rating scale reported a significant improvement for the subjects receiving chlorpromazine as compared to the subjects receiving placebo. Three of the 5 studies that used both types of measures reported a significant chlorpromazine versus placebo improvement in one of the two measures. Thus, 14 of these 23 studies reported a significant general improvement due to chlorpromazine. There was not a single report of deterioration on chlorpromazine as compared to placebo, regardless of the level of significance. The conclusion is clear: chlorpromazine produces a statistically significant improvement when measures of general change are utilized. Next in interest would ordinarily be an estimate of the magnitude of the chlorpromazine effect, that is, what percentage of subjects improve and what is the average improvement. We do not, however, consider such an estimate to be meaningful and are, therefore, not willing to make such estimates. The reasons for this opinion are presented in the section dealing with implicit methodologic factors.

An evaluation of chlorpromazine effects as measured by more or less specific measures presents some problems not in evidence when evaluating general

TABLE I. STUDIES USING GENERAL MEASURES WITH PSYCHOTIC SUBJECTS

STUDY (BY REFERENCE NUMBER)	IMPROVEMENT RATING	RATING SCALE	STUDY (BY REFERENCE NUMBER)	IMPROVEMENT RATING	RATING SCALE
1	—	Sig.	25	Sig.	—
2	—	—	26	—	NS
3	Sig.	—	27, 28	NS	—
4	NS	—	32	—	—
5	NS	NS	35	Sig.	—
6, 7	—	Sig.	38	—	—
8	—	NS	39	Sig.	—
9	Sig.	NS	40	NS	—
12	—	—	41	—	Sig.
14	NS	Sig.	42	Sig.	—
15	Sig.	NS	43	—	NS
16, 34	—	NS	44	Sig.	—
18	Sig.	—	45	NS	NS
19, 20	Sig.	—	46	—	—
24	—	—			

In this and subsequent tables, Sig. = significant drug effect, NS = drug effect not significant.

TABLE II. STUDIES USING SPECIFIC MEASURES WITH PSYCHOTIC SUBJECTS IN THE ABSENCE OF A SIGNIFICANT GENERAL EFFECT

STUDY (BY REFERENCE NUMBER)	GENERAL MEASURE	SPECIFIC MEASURES	
		NOT SIGNIFICANT	SIGNIFICANT
2	None	Memory paragraph, paired associates	
8	NS		Anxiety (interview rating)
12	None		Wechsler-Bellevue: full scale
16, 34	NS	Lorr Interview: melancholy agitation, conceptual disorganization, motor disturbances, paranoid projection, self-depreciation vs. grandiose expansiveness; Bender (Pascal-Suttell); finger dexterity; reaction time, speed: lift and jump; reaction time, variability: lift	Lorr Interview: retarded depression vs. manic excitement, perceptual distortion; weight reaction time, variability: jump
24	None	Tachistoscopic recognition of numbers	Digit symbol; pursuit rotor; tapping speed
27, 28	NS	Anxiety (Wittenborn Psychiatric Rating Scale); digit symbol; digit span; Porteus Maze; tapping and dotting	
32	None	Aggressive outbursts	Weight
38	None	Anxiety (self rating scale, psychiatric rating scale, symptom checklist); weight; CFF	
43	NS		Restlessness (Behaviour Rating Scale); tension (interview rating)
45	NS	Activity-withdrawal (Venables Activity-Withdrawal Scale)	
46	None	Pursuit rotor; verbal learning; problem solving	Cooperation (testability); Verbalized Social Adaptation Questionnaire

measures. The most important problem derives from a traditional scientific approach to theory building and data collection: precedence is given to the concepts and data with the most generality. Lacking a specific, predictive theoretic framework, data of less generality are subordinated to data of more generality. In terms of the studies under review, we are interested in specific effects of chlorpromazine which cannot be accounted for by its presumed general effects. Ideally, the procedure would involve controlling general effects either by stratification or by partialling variance. This was not done in any of the pertinent studies. The next most desirable procedure involves the evaluation of specific effects in the absence of a statistically significant general effect. This was done in 5 studies. Six studies evaluated specific effects in the absence of an evaluation

of a general effect. Thus, although not ideal for purposes of evaluation, there are 11 studies which evaluated more or less specific chlorpromazine effects in the absence of a significant general effect (Table II).

The purpose of presenting Table II is to permit a search for trends in terms of the measures per se. An examination of Table II indicates that no single measure or class of measures, however conceived, provides a consistent trend. For example, although chlorpromazine significantly reduces anxiety, restlessness, and tension in some studies, it does not do so in others; although chlorpromazine significantly increases Wechsler total scale scores, there is no effect on the Porteus Maze or on several Wechsler subtests and, in one case, chlorpromazine initiated

TABLE III. RAW DATA OF SEVERAL PARAMETERS FOR STUDIES USING A GENERAL EVALUATION WITH PSYCHOTIC SUBJECTS

STUDY (BY REFERENCE NUMBER)	GENERAL MEASURE	SAMPLE SIZE	AGE OF SUBJECTS	HOSPITALIZATION (YEARS)	DAILY DOSAGE LEVEL (MG.)	DURATION OF TREATMENT (WEEKS)
1	Sig.	34	—	—	478	17
3	Sig.	18	37	5.8	2,400	15
4	NS	20	—	New admissions	285	—
5	NS	22	46	9.0	400	12
6, 7	Sig.	20	37	10.3	800	11
8	NS	21	—	New admissions	—	2
9	Sig.	19	29	—	500	13
14	Sig.	24	50	—	150	26
15	Sig.	174	44	7.0	375	9
16, 34	NS	48	45	14.2	300	13
18	Sig.	21	—	—	—	20
19, 20	Sig.	42	34	—	100; 400	2
25	Sig.	100	—	6.6	—	6
26	NS	60	—	—	300	17
27, 28	NS	48	41	12.3	75	4
35	Sig.	57	—	—	—	17
39	Sig.	46	72	—	150; 225	4
40	NS	16	40	15.8	300	6
41	Sig.	66	45	17.0	633	12
42	Sig.	100	36	—	615	7
43	NS	24	43	15.0	300	4
44	Sig.	48	43	9.6	175	—
45	NS	44	40	12.7	300	8

a significant deterioration on the digit symbol Wechsler subtest.[24] Thus, we cannot conclude that chlorpromazine has specific effects which are marked enough to be consistently in evidence by one or more measures. This is not to say that chlorpromazine has no specific effects. It would, in fact, be surprising if specific effects were consistently found in view of the enormous variability of these studies in what are usually considered to be pertinent variables, e.g., dosage level, duration of treatment, size of sample. However, there is no *convincing* evidence of a specific effect of chlorpromazine in psychotic subjects.

Only a few of the studies reviewed above evaluated age, length of hospitalization, dosage level, or duration of medication in relation to the drug effect.

Since these are usually considered to be pertinent parameters in chemotherapy research, we felt that a coarse evaluation would be desirable as a supplement for these few studies. Accordingly, we evaluated these parameters for the 23 studies which used a measure of general change by comparing the studies which reported a significant general chlorpromazine effect with the studies which did not report such an effect. Sample size was included in these evaluations because of its general methodologic importance. Duration of illness was omitted, despite its probable relationship to length of hospitalization, because of its vagueness in concept and in presentation. The raw data are presented in Table III and the summary data are presented in Table IV. (The entry "new admissions" in Table III was not included in the summary data because of our judgment that it represents a qualitative difference from the other length of hospitalization scores. The lower dosage level was used for the 2 studies which used two different dosage level groups. This was done because our computations indicated that the lower dosage group, in both studies, contributed most to the final evaluation.)

TABLE IV. SUMMARY DATA OF SEVERAL PARAMETERS FOR STUDIES USING A GENERAL EVALUATION WITH PSYCHOTIC SUBJECTS

PARAMETER	NUMBER OF STUDIES			MEANS			MEAN SQUARES	
	TOTAL	SIG.	NS	TOTAL	SIG.	NS	WITHIN	BETWEEN
Sample size	23	14	9	46.6	54.9	33.7	1,294.43	2,476.55*
Age	16	10	6	42.6	42.7	42.5	94.69	0.15
Hospitalization	12	6	6	11.27	9.38	13.17	11.4862	42.9409†
Dosage level	19	11	8	454.5	579.6	282.5	249,781.56	408,922.19
Duration of treatment	21	13	8	10.7	12.2	8.2	39.36	78.48*

*$p = 0.20$.
†$p = 0.10$.

Table IV provides data concerning the frequency of report of these variables, average values for all the studies and for the studies according to significance or lack of significance of the drug effect, and tests of significance between the studies which demonstrated a significant drug effect and those which did not. An inspection of Table IV indicates that there are no significant differences between the two groups of studies. These results can be interpreted as being due to a true lack of relationship to the drug effect, to a curvilinear relationship, or to the operation of uncontrolled variables resulting in a heterogeneous sample. As for the age variable, these data are consistent with the data of Planansky and Heilizer[34] which indicate that the chlorpromazine versus placebo weight changes occur independently of age. (Unpublished data of the writer indicate a similar lack of relationship between age and the drug effect for all the variables in the study.) It may be of interest to note that the studies with significant results, as compared to the studies with nonsignificant results, averaged 21 more

subjects, subjects of the same age but who had been hospitalized for 4 years less, almost 300 mg. more medication, and 4 weeks longer duration. All these differences, except that for age, are what would be expected from present attitudes toward chemotherapy research. The lack of significant differences between the two groups of studies, however, prevents us from concluding a relationship between any of the above variables and a chlorpromazine effect.

Despite the paucity of studies which explicitly address themselves to the above variables, information may be gleaned from an examination of some of the individual studies. Hollister and colleagues[19,20] and Seager[39] each used two separate dosage level groups, the former using 100 mg. and 400 mg. and the latter using 150 mg. and 225 mg. Although they did not evaluate their data in terms of dosage level, in each case the data indicate a statistically significant general improvement due to chlorpromazine for the lower dosage group but not for the higher dosage group. These results are consistent with speculation by Heilizer[16] to the effect that high dosages (about 300 mg.) interfere with an improvement which occurs at lower dosages. This speculation was derived from the finding of two discrepant drug effects: (1) chlorpromazine initiated a reduced level of alertness for the group as a whole, but (2) those subjects who showed the smallest reduction of alertness tended to improve the most on the variability jump reaction time and weight measures.

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It is somewhat surprising to find three studies indicating an optimal drug effect at a rather low dosage level. Such a finding is not consistent with either present practice or the vast bulk of the clinical literature. It is especially surprising in view of the fact that the studies which reported a significant general chlorpromazine effect averaged almost 300 mg. more than the studies which did not report such an effect. We would speculate that two different systems of evaluation have been utilized. In the studies where a single dosage level was used, or where dosage level was varied individually, the criterion for improvement was, *in effect*, radical or extreme change. When two distinct dosage level groups were utilized, however, there was possible a discrimination between more extreme and less extreme changes. Where such a discrimination was possible, therefore, the less extreme changes (lower-dosage group) were judged as improvement while the more extreme changes (higher-dosage group) were judged, by comparison to the less extreme changes, as no improvement. This, of course, is speculation about data which may or may not be accepted as reliable by the reader. The speculation derives, however, from an important defect in chemotherapy research: there is a striking lack of specification and communication of what is being evaluated. This failure to specify largely limits knowledge of the actions of psychiatric drugs to a primitive and questionable body of opinion. This problem is examined at greater length in the following section.

Kornetsky and coauthors[24] also used two different dosage levels. However, their study utilized acute, rather than chronic, administration, i.e., single administration of either 100 mg. or 200 mg. with a minimum of 48 hours between administrations. They found that 100 mg. of chlorpromazine produced uniformly poorer performance than placebo and 200 mg. produced uniformly poorer

performance than 100 mg. None of the chlorpromazine versus placebo differences were significant for the 100 mg. level, three of the four were significant for the 200 mg. level (Table II), and in two measures (pursuit rotor and digit symbol) a significant impairment was yielded on the higher dose as compared to the lower dose. Thus, this study indicates (1) a consistent impairment due to chlorpromazine which (2) becomes more marked as the dosage is increased. We would speculate, as do the authors, that these results derive from the use of acute medications and reflect a generalized impairment which occurs upon initial chlorpromazine administration.

These results are consistent with the studies presented above which indicate an optimal chlorpromazine effect at a rather low dosage level. Here we find that an impairment occurs upon initial chlorpromazine medication which is more marked with higher dosages. If this initial impairment is followed by an improvement with continued medication, it is likely that a greater improvement would be evidenced at the lower dosage levels, since these entailed the least initial impairment. Further, it might be expected that the maximum improvement at each dosage level occurs earlier for the lower dosage levels as compared to the higher levels. This line of reasoning emphasizes the importance of investigating two parameters in chemotherapy investigations—dosage level and duration of medication—and the interaction between the two. Unfortunately, evaluations of these basic variables are rare.

Several studies report data which are interesting in relation to one or more characteristics of the subjects. Denber[4] and Fromm and Forsberg[8] reported a nonsignificant general drug effect with newly admitted patients. (The subjects in Denber's study were described as depressed psychotics, while Fromm and Forsberg described their subjects as mostly psychotic.) Fromm and Forsberg also reported a significant decrease in anxiety with the use of chlorpromazine. The only studies which used schizophrenic patients who have undergone lobotomy,[6,7] tubercular schizophrenic patients,[35] or aged patients with organic psychosis[39] yielded a significant general improvement on chlorpromazine. The remainder of the studies reviewed used completely or predominantly schizophrenic subjects, except for 2 which did not specify diagnostic categories.[27,28,44] Gilgash[12] used only catatonic schizophrenic subjects and reported a significant drug improvement on IQ scores. Hall and Dunlap[15] reported a greater general drug improvement for the paranoid subgroup as compared to the other subgroups. This greater improvement was statistically significant according to one set of ratings, but not so according to a second set of ratings.

Additional data of possible importance are presented in 2 studies.[15,16,34] The greatest general drug improvement occurred among subjects with the highest initial tension ratings.[15] The greatest drug improvement on variability jump reaction time occurred among the subjects with the poorest initial performance on the task,[16] although there was no relationship between improvement and initial performance on the other measures.[16,34] Improvement in ratings of contact with reality (i.e., decrease of hallucinations, delusions, and hostile impulses and improved orientation for people) were independent of all other drug-induced changes.[16,34]

PSYCHOTIC SUBJECTS: WITHDRAWAL EFFECT

The only 3 studies which investigated the chlorpromazine withdrawal effect used schizophrenic subjects. The study by Good, Sterling, and Holtzman[13] and Mefferd and co-workers[29] is by far the most impressive in conception and execution. The subject sample consisted of 112 patients who had been on continuous maintenance doses for from 34 to 514 days and had shown some improvement during treatment. They were stratified into 7 groups according to length of time on chlorpromazine at the onset of the experiment. Each group was then randomly divided into 4 subgroups according to whether chlorpromazine or placebo was administered during either or both of two successive 3-month periods: drug-drug, drug-placebo, placebo-drug, placebo-placebo. A significant general deterioration occurred during the second 3-month period among the subjects on the placebo-placebo schedule. This result suggests that it is feasible to use intermittent maintenance doses, at least on an inpatient basis. Further, the withdrawal effect was not related to the previous length of time on chlorpromazine. From this study, then, we would speculate that sequences of 1 month on chlorpromazine and 3 months on placebo are therapeutically as effective as a continuous chlorpromazine regimen. It should be indicated that the data do not necessarily indicate a return to a premedication base line upon withdrawal of chlorpromazine, but only that a significant deterioration occurred.

The remaining two studies[16,48] present data which are not consistent with the above results in that they indicate a significant withdrawal effect of relatively quick onset. The first study[16] indicates a return to the premedication base line, i.e., a reversal of the decreased alertness due to chlorpromazine, within 6 weeks. The second study[48] indicates a significant general withdrawal effect within 4 weeks. We would, however, weight the latter studies modestly in comparison to the former study, since one of them involved a good deal of nonrepresentative dropping out of subjects during the withdrawal period[16] and the other was inadequately reported.[48]

NEUROTIC SUBJECTS: DRUG EFFECT

Four studies utilized chlorpromazine in neurotic subjects.[10,11,30,37,47] Three of these studies used new admissions[10,11,30,47] and one study used outpatients.[37] No significant differences were found between chlorpromazine and placebo on a variety of evaluative procedures. Thus, we conclude that there is no evidence of a chlorpromazine effect when neurotic subjects are used.

Before concluding that there is no chlorpromazine effect, however, it is pertinent to mention that these studies averaged only 3.2 weeks in duration with an average daily dosage of 193.7 mg. (Table V). A comparison of these figures with the data presented in Table IV indicates that these studies averaged 260.8 mg. less daily chlorpromazine dosage and were 7.5 weeks shorter in duration. The review of the drug effect in psychotic subjects indicates that a general impairment may occur upon initial chlorpromazine administration, to be followed by a general improvement upon continued medication. It is possible, therefore, that these studies, using continuous medication but for relatively short durations,

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are evaluating two separate effects in such a proportion as to eliminate an over-all effect. Although this possibility is clearly speculative, its plausibility serves to inhibit the conclusion that there is no chlorpromazine effect when neurotic subjects are used and serves to facilitate the conclusion that there is not enough evidence for a decision.

It is, in fact, possible that chlorpromazine produces undesirable effects among neurotics. Raymond and colleagues[37] report that 6 of their 42 subjects refused chlorpromazine medication after 3 to 6 days because of undesirable effects. Since there were no similar refusals for any of five other medications, it might be concluded that there was a significant deterioration due to chlorpromazine. Here, too, however, the possibility of an initial impairment inhibits any definitive conclusions.

TABLE V. RAW DATA OF SEVERAL PARAMETERS FOR STUDIES USING NEUROTIC SUBJECTS

STUDY (BY REFERENCE NUMBER)	SAMPLE SIZE	AGE (YEARS)	HOSPITALIZATION	DAILY DOSAGE (MG.)	DURATION OF TREATMENT (WEEKS)
10, 11	39	25	New admissions	ca. 200	6
30	21	—	New admissions	ca. 225	4
47	59	33	New admissions	200	1
37	42	—	Outpatients	150	2
Mean	40.2	29		193.7	3.2

NORMAL SUBJECTS: DRUG EFFECT

Two studies used chlorpromazine with normal subjects.[21-23,31,36] Both studies used acute medications at two dosage levels and a wide variety of evaluative procedures. Their results indicate a consistent impairment due to chlorpromazine which becomes more marked with increasing dosage level. These results are similar to the data reported by Kornetsky and coauthors[24] with schizophrenic subjects. Insofar as these few comparable studies indicate, therefore, results are similar for schizophrenic and normal subjects.

SUMMARY

The clearest conclusion is that chlorpromazine has a salutary general effect upon psychotic subjects; there is no convincing evidence that it has one or more specific effects. There is no evidence of a chlorpromazine effect with neurotic subjects. There is some evidence for two paradoxical drug effects: (1) an optimal improvement occurring at a daily dose of 100 to 200 mg., which is followed by a relative impairment as dosage level is increased; (2) an initial impairment which is followed by improvement as medication is continued. There is no evidence that the drug effect is related to age or length of hospitalization, although it may be that subjects with the highest initial tension or poorest initial performance

benefit the most from chlorpromazine medication. The most satisfactory data on withdrawal effects indicate a persistence of the drug effect for from 3 to 6 months after withdrawal. They further indicate that the withdrawal effect is independent of duration of previous medication within wide limits.

Implicit Methodologic Variables

GENERAL MEASURES

In the previous section it was stated that estimates of percentage improvement and average improvement are not meaningful when measures of general change are used. This judgment is based on an examination of two pertinent measurement procedures: the behavior ratings and the observational system.

The types of behavior to be rated are more or less specified when rating scales are used, while there is a near absence of specification when improvement ratings are used. These procedures contain important implications. Thus, rating scales satisfy the criterion of scientific communicability to a much greater extent than do improvement ratings. In fact, improvement ratings are often used because they are not restricted to a certain number of a priori specified types of behavior. This lack of standardization is intended to produce a rating which is highly sensitive to any changes which may occur; it permits an a posteriori focus upon the most noticeable changes. Although this increased sensitivity is an artifact of an a posteriori rating system, it is nevertheless highly valued by many investigators.

The observational system is generally not specified for either measurement procedure; it is apparently determined by the observers themselves. There has been almost no mention of standard periods of the day when observations were made, standard activities, standard lengths of observation, etc. This lack of standardization of observational systems encourages the action of subjective and uncontrolled variables in both improvement ratings and rating scales. The most important faults of this procedure are a lack of comparability among observations and evaluations which are derived from a heterogeneous and poorly understood series of procedures.

Regarding the lack of standardization as seriously as we do, it seemed desirable to attempt an initial research evaluation within the limits of the data of this review. Size of sample was selected as the independent variable because the data were easily available and the variable permitted a rational derivation and subsequent predictions and evaluations.

It is a common observation that the more work there is to be done, the more time is required. If the amount of work is increased but no compensatory time is provided, a deterioration of quality is likely to result. If, on the other hand, each work unit inflexibly requires a certain amount of time, a compensatory increase in time must occur for a given increment in work. In the former example, the units of work are not standardized. As a result, an increase in quantity is made possible by a concurrent decrease in quality. In the latter example, the units of work are standardized. As a result, an increase in quantity does not

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occur at the expense of a decrease in quality; an increase in quantity occurs only at the expense of an increase in time. The former procedure might be labelled *quantity control* while the latter might be labelled *quality control.* An emphasis on quality control, achieved through rigid standardization, is an important scientific tradition. The general use of unstandardized conditions in chemotherapy investigations, however, is analogous to the quantity-control procedure. In referring the terms *quantity* and *quality* to the following analysis, the former is equated with the size of the sample and the latter with the efficiency of isolating chlorpromazine-induced general improvement, i.e., the percentage of subjects judged to improve on chlorpromazine minus the percentage of subjects judged to improve on placebo. Thus, on the basis of this analogy, it can be predicted that an increase in sample size will result in a decrease in reported chlorpromazine-induced improvement.

An attempt to isolate the variables potentially responsible for such a prediction is not very satisfying. It is possible that the analogy may pertain directly, i.e., an increase in sample size simply reduces the per capita time available for observing and/or rating. It is also possible that the analogy may only pertain indirectly, in that a series of intervening effects are the responsible agents. For example, an increase in the size of the sample might render the observer's role more impersonal, reduce the personnel's interest in the investigation, or change an initially positive attitude toward drugs to an eventually negative attitude. A proper evaluation of such variables requires investigations which focus directly upon the selected concepts. In the absence of such investigations, we were able to utilize two variables which were consistently reported in the literature and which are pertinent to the prediction.

The first variable involves the distinction between studies which evaluated only chlorpromazine (single evaluation studies) and studies which evaluated one or more medications in addition to chlorpromazine (multiple evaluation studies). At any given sample size, as presented in this review, a multiple evaluation study actually utilized a larger sample than did a single evaluation study, because of the omission of subjects receiving nonchlorpromazine experimental medication in our evaluations. Thus, for comparable chlorpromazine and placebo sample sizes, the multiple evaluation studies should report less chlorpromazine-induced improvement than the single evaluation studies. Further, we would expect that the predicted negative relationship between sample size and chlorpromazine-induced improvement will be attenuated for the multiple evaluation studies as compared to the single evaluation studies. This expectation derives from the belief that a study which evaluates several systems is inherently more diffuse than a study which evaluates one system. When a multiple system evaluation is used, this diffusion of interest, effort, observation, etc., attenuates any relationship which occurs for a single system, evaluated individually.

The second variable involves the distinction between improvement ratings and rating scales. As described above, improvement ratings are expected to be less standardized and more sensitive than rating scales. We would expect that the difference in standardization of the two evaluation procedures will permit

a greater negative relationship between sample size and reported chlorpromazine-induced improvement when improvement ratings are used. Further, we would expect that the difference in sensitivity will result in the reporting of a smaller chlorpromazine-induced improvement when rating scales are used.

A total of 18 studies provided data which are pertinent to this line of inquiry.[3-9,15,18-20,25,27,28,35,39-42,44,45] These studies used improvement ratings or/and rating scales as measures of general improvement with psychotic subjects and

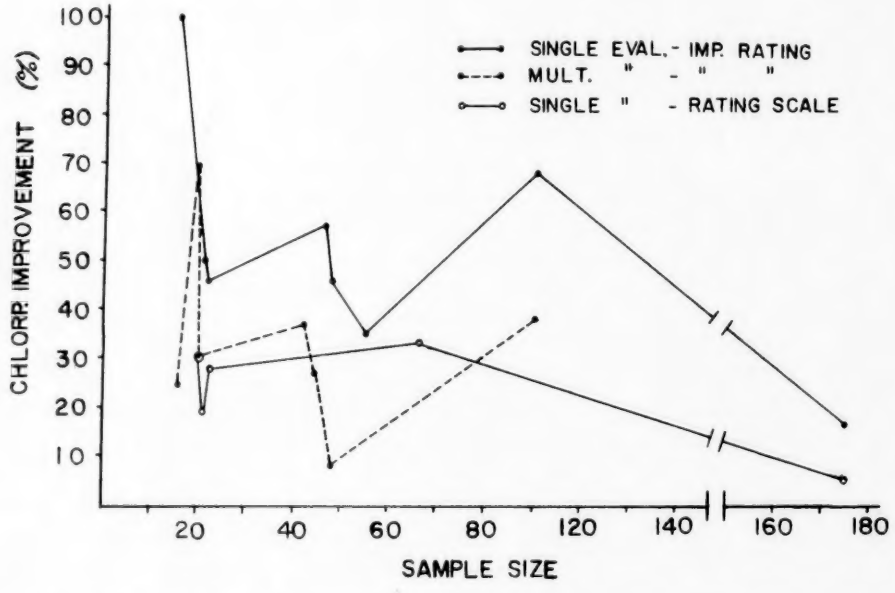

Fig. 1. Per cent of patients showing chlorpromazine-induced general improvement as a function of sample size.

either reported their results in terms of chlorpromazine-induced improvement or presented the frequency data, thus permitting the computations to be made. Eight single evaluation studies and 7 multiple evaluation studies used improvement ratings; 5 single evaluation studies and 1 multiple evaluation study used rating scales. (Two single evaluation studies and 1 multiple evaluation study used both a rating scale and an improvement rating, resulting in an apparent total of 21 studies.) Thus, there are enough studies available for statistical evaluations in three categories: single evaluation studies using improvement ratings, multiple evaluation studies using improvement ratings, and single evaluation studies using rating scales. We are predicting: (1) a negative correlation between sample size and chlorpromazine improvement for the single evaluation–improvement rating studies; (2) an attenuation of this correlation for the multiple evaluation–improvement rating studies and the single evaluation–rating scale studies; (3) a general reduction of chlorpromazine-induced improvement for the

multiple evaluation–improvement rating studies and single evaluation–rating scale studies as compared to the single evaluation–improvement rating studies.

The pertinent raw data are charted in Fig. 1 and the summary data are presented in Table VI. (The study which utilized 174 subjects was omitted from category 1 of Table VI when the *t*-test between categories 1 and 2 was computed. The comparison of means required approximately equal sample sizes, within the context of the rationale, and there was no study in category 2 which approximated a sample of 174 subjects.) The data are consistent in direction with predictions 1 and 3, but are ambiguous in relation to prediction 2, inasmuch as the two estimates of relationship differ widely for the single evaluation–rating scale studies. In terms of statistical significance, the data permit rejection of the null hypothesis for prediction 3, but not for predictions 1 or 2. In terms of gross impressions, there is a striking similarity between the shapes of the curves for the 2 groups of studies which used improvement ratings and there is a wide range of mean chlorpromazine improvement among the several groups.

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Objective scientists may differ in their evaluation of data, and these data are no exception. We feel, however, that these data provide, at the minimum, an overview of the foundations of chemotherapy research, and the foundations are unstable, at best.

TABLE VI. SUMMARY DATA FOR CHLORPROMAZINE IMPROVEMENT ACCORDING TO SAMPLE SIZE, TYPE OF EVALUATION, AND TYPE OF RATING

CATEGORIES	NUMBER OF STUDIES	SAMPLE SIZE AND DRUG IMPROVEMENT		MEAN	S.S.	T-TEST
		PEARSON R	RANK R			
1a. Single Evaluation-Improvement Rating	8	−0.54*	−0.54*	52.62	4,034.62	1a. vs. 3.: 2.56†
1b. Single Evaluation-Improvement Rating	7	—	—	57.43	2,743.71	1b. vs. 2.: 2.24†
2. Multiple Evaluation-Improvement Rating	7	−0.13	−0.04	33.43	2,069.86	—
3. Single Evaluation-Rating Scale	5	−0.77*	−0.30	23.00	514.00	—

*$p = 0.20$.
†$p = 0.05$.

OTHER VARIABLES

In addition to the lack of standardization and comparability among general measures, there are many implicit attitudes and methodologies of potential importance to chemotherapy research. The most striking of these cannot be examined within the context of this review since the studies selected for inclusion have been stratified according to the pertinent variables, i.e., the selection criteria for this review. Furthermore, a wide variability in the reporting of certain

procedures, or a lack of such reports, prevents the examination of these procedures, e.g., the concept of the "double blind" investigation or seasonal variations of hospital activities. However, we have been able to select five variables for rational and empirical presentation, on the rational grounds that they are of potential interest or importance and on the empirical grounds that they are presented in all of the 23 studies which used a general measure to evaluate the drug effect with psychotic subjects. Our purpose is to indicate variables of possible pertinence to chemotherapy research, to rationalize them in the sense of indicating some reasons for the judgment of pertinence, and to gather and report data of a preliminary nature. Although value judgments may be evident in some of what follows, there is no attempt to make specific predictions; although the data are presented in a statistical fashion, there is no attempt to evaluate or interpret by generalizing to a population. Our primary intention is to present and rationalize certain variables and report sample-descriptive data in the hope that it will be of use to the reader.

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The first variable, partially presented in the preceding subsection, is the type of evaluation, i.e., single evaluation studies versus multiple evaluation studies. Fourteen studies were of the single evaluation type while 9 studies involved multiple evaluations. An investigator may be interested in evaluating one drug or he may be interested in evaluating and comparing several drugs. The single evaluation study is relatively simple and direct in both conception and execution. The multiple evaluation study is relatively more complex and cumbersome. It involves: evaluation of each medication and comparisons among medications; problems such as optimal dosage levels for the various medications in order to render them comparable; various medications with a subsequently increased heterogeneity of behavioral changes; etc. The added demands placed upon a multiple evaluation study may be expected to affect all components of the study, resulting in a more diffuse interest on the part of the investigators and a less satisfactory experiment. For example, 62 per cent of the multiple evaluation studies (13 out of 21) in the Appendix used a crossover design to investigate the drug effect, as compared to 26 per cent of the single evaluation studies (7 out of 27).

The second variable is the sex of the subjects. Six studies used only male subjects, 11 studies used only female subjects, and 6 studies used male and female subjects in varying ratios. This variable was not included in Tables III and IV of the first section because we wished to emphasize certain conditions which are confounded with the sex of the subjects in chemotherapy research. (However, this does not preclude the operation of sex as a variable in its own right, be it interpreted in biologic, psychologic, or sociologic terms.) The most noticeable relevant condition is the type of hospital to which men and women are admitted. Women may be admitted to state, municipal, territorial, and private hospitals, but not to Veterans Administration neuropsychiatric (NP) hospitals. Men, on the other hand, may be admitted to any of these hospitals. Thus, studies utilizing women will not have been conducted in V.A. NP hospitals; they are most likely to occur in the various state hospital systems. A comparison of the V.A. hospital

system with the various state hospital systems throughout the country clearly favors the former in terms of expenditures, equipment, etc. Differences in the selection and treatment of patients and the attitudes and training of personnel might be expected to occur. Another relevant condition might involve differences in treatment between males and females in the same hospital. Since hospital wards are segregated by sex, there will likely be increased heterogeneity for studies using subjects of both sexes as compared to studies using subjects of either sex alone. In the long run, we would expect that the former studies involve more personnel, greater differences in the experiences and attitudes of the personnel among the various wards, greater differences among the activities and therapies of the patients among the various wards, etc. Another relevant condition might involve national differences in hospital systems, e.g., British versus American, and the concomitant and resultant differences in selection of patients for hospitalization and for inclusion as subjects, treatment programs, etc. Paradoxically, it may be that sex differences are only partially responsible for sex differences in chemotherapy research.

The third variable is the dispensing of medications, i.e., individual medications in which the medications are dispensed in individual containers versus group medications in which a group dispensing system is used. Eight studies used individual medications and 15 studies used group medications. Dispensing medications in individual containers may be considered a central procedure to the double-blind investigation. Thus, its use or nonuse is directly related to attitudes towards the double-blind control procedure and, by inference, to scientific methodology in general. The investigator must consider the procedure to be of some importance in order to expend the additional time and energy necessary to utilize it. Further, the attitudes implicit in the use of individual medications are in marked contrast to the attitudes of the many investigators who simply equate the use of a placebo control with a double-blind control.

The fourth variable is the medication schedule, i.e., constant schedules in which a single dosage level is used for all subjects, standard schedules in which the dosage level is varied for all subjects concurrently, and individual schedules in which dosage levels are varied individually. Eight studies used a constant schedule, 5 studies used a standard schedule, and 10 studies used individual schedules. A basic methodologic distinction is involved in the use of constant or standard schedules as compared to individual schedules: the utilization of a priori criteria in the former as compared to the use of a posteriori criteria in the latter. The use of a posteriori criteria and manipulations vitiates the procedures of science with a multitude of corrupting effects. The primary intent in the use of individual medication schedules is to produce the maximum possible improvement for each subject with the medication which is being evaluated. This requires intensive observation of and interaction with each subject, as well as a judgment, for each subject individually, as to maximum improvement and optimal dosage level. Further, it necessitates a series of intermediate, personal, unspecified judgments during the course of the investigation, leading finally to a judgment of over-all improvement which is, in effect, an endorsement of the preceding series of judgments. It is possible that such a procedure may produce

a highly sensitive evaluation of the medication under certain circumstances of scientific controls in which the criteria are formulated and executed a priori. It is more likely, however, that this procedure, as presently utilized, produces a highly sensitive evaluation of the investigator's behavior by maximizing the operation of his biases. (It might even be considered tautologic, beginning and ending with the investigator's evaluations.) For example, an investigator who is enthusiastic toward the chemotherapeutic approach, as compared to a less enthusiastic investigator, can be expected to increase dosage levels more rapidly, utilize an ultimately greater dosage, foster more constant observation and more intense interaction, etc. Additionally, this procedure is anathema to the concept of the double-blind investigation. The utilization of constant observation and a series of aperiodic, unstandardized judgments will necessarily minimize the investigator's ignorance of the medication prescriptions when individual medications are used; when group medications are used the double-blind edifice will be leveled.

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A second distinction to be made with respect to the selection of a particular medication schedule is involved in the use of constant schedules as compared to standard schedules. When a priori decisions are made concerning dosage levels, the selection of the latter procedure emphasizes certain clinical values. The use of an increasing-dosage standard schedule emphasizes the possible occurrence and importance of undesirable side effects; the attempt is made to minimize such occurrences by providing for adaptation to the medication at initially lower dosage levels before a presumably effective or optimal level is reached. The use of a decreasing-dosage standard schedule emphasizes the possible occurrence and importance of undesirable withdrawal effects, i.e., an addiction effect or/and relapse; the attempt is made to minimize such occurrences by providing for adaptation to the absence of medication at subsequently lower dosage levels after a presumably effective or optimal level has been reached. Parenthetically, it may be noted that Heistad[17] predicts, by application of the concept of stimulus generalization, a relatively greater therapeutic action for a given medication when constant schedules are used than when standard schedules are used. At this writing, neither the clinically accepted values of the standard schedule nor the putative effectiveness of the constant schedule has been evaluated.

The fifth variable is the national origin of the investigation, i.e., studies conducted in America versus studies conducted in England. There were 16 American studies and 7 British studies (including one Canadian study). It may be stated as a general working hypothesis that the data of the behavioral sciences are, to some undefined degree, relative to the culture. Comparisons among cultures are therefore generally in order. This is especially true of chemotherapy research since differences in national attitudes towards mental illness and the value of chemotherapy are involved.

The summary data for these variables are presented in Tables VII and VIII. The frequency data of Table VII were evaluated by an exact probability procedure,[33] except for the analysis which contained four *df* (Sex of Subjects with Medication Schedule) for which chi square was used. The evaluations of the

methodologic variables by significance level, type of evaluation, and significance level times type of evaluation are analogous to a 2 times 2 analysis of variance. They were computed, despite the laboriousness of the procedure and the small number of studies, because of our interest in the type of evaluation as a relatively important variable. The mean data of Table VIII were evaluated by randomized analyses of variance. These evaluations are recoverable in conjunction with the data of Table IV.

SUMMARY

The primary concern of this section has been to make explicit certain implicit methodologic variables: the process of observing and recording behavior,

TABLE VII. FREQUENCY DATA FOR IMPLICIT METHODOLOGIC VARIABLES

IMPLICIT METHODOLOGIC VARIABLES			TYPE OF EVALUATION		SEX OF SUBJECTS			MEDICATION DISPENSED		MEDICATION SCHEDULE			NATIONALITY	
			M	S	F	MF	M	G	I	I	S	C	BRITISH	AMERICAN
Significance level	Sig.		3	11*	8	3	3	10	4	9	2	3†	3	11
	NS		6	3	3	3	3	5	4	1	3	5	4	5
Type of evaluation	Single (S)				8	2	4	8	6	9	2	3†	3	11
	Multiple (M)				3	4	2	7	2	1	3	5	4	5
Type of evaluation	Single	Sig.			8	2	1‡	7	4	8	1	2	3	8
×		NS			0	0	3	1	2	1	1	1	0	3
Significance Level	Multiple	Sig.			0	1	2	3	0	1	1	1	0	3
		NS			3	3	0	4	2	0	2	4	4	2
Sex of subjects	Male (M)							3	3	1	3	2	0	6*
	Male and Female (MF)							5	1	3	0	3	1	5
	Female (F)							7	4	6	2	3	6	5
Medication dispensed	Individual (I)									3	3	2	3	5
	Group (G)									7	2	6	4	11
Medication schedule	Constant (C)												4	4§
	Standard (S)												2	3
	Individual (I)												1	9

*$p = 0.08$
†$p = 0.04$
‡$p = 0.01$
§$p = 0.13$

TABLE VIII. MEAN DATA OF SEVERAL PARAMETERS FOR IMPLICIT METHODOLOGIC VARIABLES

IMPLICIT METHODOLOGIC VARIABLES		SAMPLE SIZE		AGE OF SUBJECTS		HOSPITALIZATION (YEARS)		DOSAGE LEVEL (MG.)		DURATION OF TREATMENT (WEEKS)	
		NUMBER	MEAN	NUMBER	MEAN	NUMBER	MEAN	NUMBER	MEAN	NUMBER	MEAN
Type of evaluation	Single	14	49.9	10	45.5*	7	10.41	11	588.7*	13	12.7†
	Multiple	9	41.4	6	37.8	5	12.48	8	270.0	8	7.5
Sex of subjects	Male	6	28.7‡	5	38.2	3	11.17	5	420.0	6	8.8
	Male and Female	6	76.5	2	42.5	3	8.63	4	258.7	5	10.6
	Female	11	40.1	9	45.1	6	12.65	10	550.1	10	11.9
Medication dispensed	Individual	8	33.2	6	43.2	5	12.26	6	393.0	8	11.9
	Group	15	53.7	10	42.3	7	10.57	13	482.9	13	10.0
Medication schedule	Constant	8	38.0*	6	47.0	3	14.10	8	207.5*	7	10.3
	Standard	5	25.8	5	39.0	4	11.75	5	460.0	5	9.6
	Individual	10	63.9	5	41.0	5	9.20	6	779.3	9	11.7
Nationality	American	16	51.4	9	39.2*	7	9.99*	12	598.8*	15	11.5
	British	7	35.7	7	47.0	5	13.08	7	207.1	6	8.7

*$p = 0.20$
†$p = 0.10$
‡$p = 0.05$

type of evaluation, sex of subjects, dispensing of medications, medication schedules, and the national origin of the investigation. Pertinent data were computed utilizing the studies from the first section which evaluated the drug effect with psychotic subjects by means of a general measure.

DISCUSSION

The most startling finding of this review is that only 37 studies meet certain minimum standards of scientific evaluation. The conclusion seems warranted that clinical chemotherapy investigators have not generally assimilated basic scientific standards. This is the more surprising since a large number of publications, dealing with various aspects of the research process, are available in the pertinent professional literature. It appears, therefore, that this situation is due to a resistance to the use of scientific methods. Further, in order for such a situation to exist, it must be at least accepted by the domain of interested parties, e.g., research groups, funding foundations, drug houses, journal editors, etc. This problem is too important for our understanding of behavior and the treat-

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ment of patients to be honored in the breach. The following presentation may be considered as a banner, a target, or simply an attempt limited by contingencies of experience, training, and bias to contribute to the evolution of the art and the science. It is to be hoped that more light than heat is generated, though some of each is desirable.

CLINICIAN VERSUS SCIENTIST*

Central to an understanding of the problem is the traditional schism between clinician and scientist. The clinician ministers to the sick utilizing whatever information and procedures are available. Decisions of diagnosis and therapy are continually made because the situation demands such decisions. Were the clinician to wait upon scientifically certified procedures, the profession would cease to exist. Furthermore, our culture requires the clinician to minister with assurance and conviction. This requirement emphasizes the application of knowledge while de-emphasizing the methodology of knowledge. As a result, the clinician's methodology of knowledge is derived from his application of knowledge: his personal experiences and the experiences of his colleagues. This informal and highly personalized procedure produces a wide variability among individuals in what is judged as known and thus applied. Such a procedure also produces styles of treatments, namely, an enthusiastic acceptance of a particular treatment followed by a growing skepticism followed by an enthusiastic acceptance of another treatment, etc., resulting, in the extreme instance, in the widespread existence of such an ethically dubious procedure as irreversible brain damage by surgery.

The scientist, on the other hand, is a specialist in the methodology of knowledge. His responsibility for the application of knowledge is secondary and is largely nonexistent in his formative years of training. The expectations of our society for the scientist are relatively vague and unformulated, with a corresponding decrease of specific requirements and pressures for the application of knowledge. Thus, decisions pertaining to the methodology of knowledge can be and are made in accordance with relatively formal and exacting principles. Additionally, however, the scientific community requires the scientist to operate intensively in the acquisition of knowledge, i.e., publish or perish. This requirement produces styles of research and theory, e.g., an enthusiastic interest in a particular method or concept followed by a growing lassitude followed by an enthusiastic interest in another method or concept, etc., resulting, in the extreme instance, in the occurrence of a semiofficial "religion" which simply lapses into limbo with the coming of a new generation.

What expectations would we have were the roles reversed? Let us assume that a scientist is selected "Clinician for a Day." He would be required to utilize knowledge which, by his standards, does not exist. He would find himself resorting to opinions, personal experiences, authorities, etc., with a bewildering diversity

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of possible decisions. When entering his decisions in the competition of ideas, he would discover that his formal and exacting principles are inappropriate in an arena where informal procedures and personal experiences prevail; his most precise formulations and logical objections would be greeted by the terse comment, "It works!" We would expect him to end his day with a sigh of relief and a statement to the effect that, "These blunderers don't know what they are doing."

Let us assume, on the other hand, that a clinician is selected "Scientist for a Day." He would be required to focus upon the limitations and fallibility of knowledge which, by his standards, is perfectly adequate. He would find himself immersed in intricate intellectual pirouettes and picayune details with a frustrating stifling of eventual action. When entering his decisions in the competition of ideas, he would discover that his informal procedures and personal experiences are inappropriate in an arena where formal and exacting principles prevail; his most sensitive observations and articulate recommendations would be greeted by the terse comment, "Prove it!" We would expect him to end his day with a sigh of relief and a statement to the effect that, "These dreamers can't accomplish anything."

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The situations described above appear to be typical of contemporary attitudes and orientations. Each discipline has evolved with respect to a particular environment which is at least partially exclusive of the other. It is not to be expected that a creature of one environment will function optimally in an alien environment. Yet, an important result of lumping all investigatory activity under the title of "research" is to encourage the scientist and pressure the clinician to attempt the combined role of scientist-clinician. It is our impression that this combination of roles has worked poorly; it emphasizes the methodology of knowledge at the expense of the application of knowledge, with the result that a widespread reaction has occurred which emphasizes the application of knowledge at the expense of the methodology of knowledge. The net effect has been detrimental to the work of both disciplines. Thus, the scientific literature, as reflected by the 37 studies reported here, is not especially noteworthy in terms of such scientific emphases as formulation and evaluation of hypotheses, design, instrumentation, etc.; while the clinical literature, as reflected by the total of 500 to 600 studies reviewed by the author, is not especially noteworthy in terms of such clinical emphases as indications for therapy, therapeutic specificity, dosage level, trained clinical observation, etc.

It appears that the contemporary emphasis on togetherness by conscription is misplaced and results in mutual antagonism and defensiveness rather than a symbiotic productivity. The emphasis is profound and multifaceted, deriving from our notion of the complete citizen, comfortably accomplished in many areas. It appears in graduate schools and medical schools, at meetings, and in the literature as an emphasis on the techniques of science and the incompleteness of clinical techniques. It is an intrusion upon the professional development of both clinician and scientist because it offers competing ideas in a destructive manner, i.e., in a setting which largely ignores the distinctive image of each discipline. Each discipline must have prior understanding of the nature of its own

adaptive functioning and acceptance of the limitations for the development of a productive common effort. Such prior acceptance would involve initially separate programs and philosophies. Only after the methods and values of the discipline had been thoroughly integrated would the methods and values of the other discipline be learned.

The development of two distinct, secure disciplines would provide a potential for development which is improbable under present conditions. A recognition of the differing aims of each discipline would permit clearer definitions of various activities in relation to a particular discipline. Thus, an investigator might formulate his activities in relation to the methods and goals of the clinician or the scientist or the scientist-clinician. More clearly defined activites would eventually evolve more efficient and more precise communication networks. The net result would be a greater perspective, higher professional standards of activity, and a more natural and productive development of knowledge according to the separate needs of methodology and application.

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DEMAND BEHAVIOR

A specific illustration of the differences between the two disciplines may be taken from their responses toward the behavior of subjects. A cardinal principle of scientific research requires that interactions between the subject and the experimenter occur in a manner which is specified as completely as possible before the start of the experiment. A cardinal principle of clinical practice is that interactions between the patient and the clinician must occur largely in an emergent and undefined manner. The clinician uses the term "patient," indicating a primary interest in treatment, while the scientist uses the term "subject," indicating a primary interest in observation. The clinician regards the patient's behavior as demanding responses of a therapeutic nature, while the scientist regards the subject's behavior as demanding responses of a recording nature. Thus, behavior demands interference from the clinician and noninterference from the scientist.

These principles and the related attitudes are reflected in the nature of their respective research. Assume, for example, that the intention is to determine the optimal dosage level of a particular medication. The clinician will vary the dosage for each patient individually, while the scientist will assign each subject to one of several constant dosage level groups. They are only apparently asking the same question. In actuality, the clinician is attempting to produce a maximum improvement in all his patients and infer the relative efficacy of various dosage levels; the scientist is attempting to determine the optimal dosage level directly, but without regard to individual differences among his subjects. While it is important to emphasize the deficiencies of the former procedure in terms of scientific methodology (see the previous discussion of medication schedules), it is also important to emphasize the limitations of the latter procedure in regard to the clinical purpose. A scientific procedure cannot justifiably claim general primacy over a clinical procedure unless it can deal effectively with the clinical purpose as well as with its own purpose. In this instance, the scientist would have to incorporate the clinical interference demanded by the patient's behavior

into the research design, thus coming to grips with the problem of individual differences in the clinical setting. The experimental design would be elaborate because of the precautions which are required in order to satisfy the demands of both disciplines. For example, each subject might be assigned to one of several dosage level groups. The dosage could then be varied for individual subjects according to clinical judgments. The dosage adjustments would occur at specified intervals, within specified limits, and in specified units. The scientific controls would be generated within each set of clinical judgments, in that a certain proportion of the clinical recommendations would be consummated while corresponding proportions would receive alternate programs. The interests and requirements of both disciplines would be satisfied.

Similar procedures can be derived for other problems of common interest. The basic requirement for such procedures would be the utilization of the best which each discipline offers rather than something less, as in the past.

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48. Zeller, W. W., Graffagnino, P. N., Cullen, C. F., and Rietman, H. J.: Use of Chlorpromazine and Reserpine in the Treatment of Emotional Disorders, J. A. M. A. **160**:179, 1956.

APPENDIX

ANNOTATED BIBLIOGRAPHY*

The purpose of this bibliography is to summarize experiments on the effects of chlorpromazine upon adult schizophrenics. Our minimal criterion of "experimental investigation" is the concomitant administration of chlorpromazine and placebo. Where a study is composed of various segments, some of which meet this criterion and some of which do not, the summary is primarily directed toward the segments which meet the criterion. Further, the use of a "pure unknown" is required, i.e., a combination of chlorpromazine with another medication is considered beyond the scope of this bibliography. Our interest in adult schizophrenics is limited to behavior variously labeled psychologic, psychiatric, and/or overt. Where a study investigates these types of behavior, as well as other behavior, only the former are included. Our conceptualization of schizophrenia requires the inclusion of studies which utilize subjects along a continuum of adjustment, i.e., normal and neurotic persons as well as schizophrenics.

The bibliography consists of two sections. Section 1 contains those studies which utilized only chlorpromazine and placebo. Section 2 contains those studies which utilized one or more medications in addition to chlorpromazine and placebo. Thus, the context of the two sections is markedly different: the studies contained in Section 1 are directly pertinent to the purpose of this bibliography, while the studies contained in Section 2 are of indirect pertinence. As a result, the studies of Section 1 are more completely and more consistently summarized than are the studies of Section 2.

Throughout the bibliography, a single summary is presented where two or more studies were conducted with the same subjects or where two or more articles describe the same study.

The summaries are organized according to six categories: hypothesis or interest (HI), subjects (Ss), medication (Med), design (Des), instruments (Inst), and results or conclusions (RC). In addition, a seventh category, comments (Com), is often included. A brief description of terms and abbreviations follows:

HI *General* refers to a general statement of interest by the experimenters or to the lack of a specific statement of interest.

Ss M = average (mean or median); R = range; SD = standard deviation; *Hosp* = length of hospitalization; *app* = approximately and is used to indicate that an estimate is being made; all references to time are in years unless otherwise stated.

Med An asterisk (*) indicates that medications were dispensed in individual containers; *schedule* refers to the method utilized in determining dosage level, i.e., *constant* (a single dosage level for the entire sample), *standard* (dosage levels were varied for the entire sample, presumably according to a prearranged plan), *individual* (dosage levels were varied individually); E = experimental (chlorpromazine); C = control (placebo); *mg.* = mg./day; oral administration was used unless otherwise stated.

Des *Linear* refers to two concomitant drug groups (chlorpromazine and placebo); *Crossover* refers to a change of medication for all or part of the two concomitant drug groups.

RC E/C indicates that an experimental versus control comparison or conclusion was made.

There are two important omissions in the summaries: side effects and the "double blind." Although of major importance, they are not included because of the uneven descriptions presented in the literature, the lack of E/C evaluations for the former, and the complexity of the latter. Reference is made to the concept of the "double blind" by indicating the studies in which medications were dispensed in individual containers and by indicating the personnel involved in interviews and ward behavior ratings.

SECTION 1

Abrams, J.: Chlorpromazine in the Treatment of Chronic Schizophrenia, Dis. Nerv. System 19: 20-28, 1958.

HI (a) Logical thinking, (b) anxiety and hostility, (c) overt behavior.

*We would like to thank Dr. Benjamin McNeal of the V. A. Hospital at Canandaigua, N.Y., and Drs. Isidor Scherer and Arnold Trehub of this hospital for providing the time and resources for the completion of the following bibliography.

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Ss 34 female schizophrenics. Age: R = 20 to 55. Hosp: minimum of 2 years.

Med Constant schedule of 200 mg. for the first week. Individual schedules thereafter with a maximum of 400 mg. for 11 E subjects and all C subjects and a maximum of 600 mg. for 7 E subjects. Total duration of 4 months with all subjects on maximum dosage for at least 2 months.

Des Linear design. Pre- and post-testing.

Inst (a) Wechsler-Bellevue Intelligence Scale; (b) Rorschach: scored for anxiety and hostility by four judges according to the Elizur method; (c) Lorr Multidimensional Scale for Rating Psychiatric Patients (MSRPP): interviews were conducted by the ward psychiatrist; ward behavior was rated by the nurse or attendant.

RC (a) Lorr: significant E/C improvement on total morbidity, F (perceptual distortion), G (motor disturbances), K (conceptual disorganization), and I (withdrawal); significant E/C increase in submissiveness (H). (b) Significant E/C improvement on the similarities subtest of the Wechsler.

Com Evaluation of E/C differences was done for the post-testing scores only. If the E/C evaluations are computed from pre-post difference scores for each group, the following results: (a) Similar results are obtained on the F, G, K, and H scales of the Lorr as well as for the total morbidity measure; (b) in addition, significant E/C improvement occurs on B (compliance versus resistiveness), C (paranoid projection), and J (self-depreciation versus grandiose expansiveness); (c) there is no significant E/C difference on the similarities subtest of the Wechsler or on the I factor of the Lorr Scale.

Cutler, R. P., Monroe, J. J., and Anderson, T. E.: Effects of "Tranquilizers" Upon Pathological Activity in Psychotic Patients: I. Chlorpromazine, A. M. A. Arch. Neurol. & Psychiat. 77: 616-622, 1957.

HI (a) Pathologic activity (general), (b) relationship between pathologic activity and somnolent behavior.

Ss 12 male schizophrenics. Age: R = 27 to 64. Length of illness: M = 16.6, R = 3 to 44. Two subjects had undergone lobotomy.

Med Standard schedule for the first 4 days of each stage, going from 200 mg. to 600 mg. Constant schedule of 600 mg. therafter. Total duration of 6 weeks for each stage.

Des Crossover design. Continuous observations. The experiment consisted of four stages: (a) 3-week pre-experimental period, during which no medications were given, to gather stabilized base-line data; (b) 6 weeks during which the subjects received either chlorpromazine or placebo; (c) 6 weeks during which all subjects received placebo; (d) 6 weeks during which the medication of (b) was reversed. In addition, a follow-up experiment, consisting of three stages, was utilized: (a) 10 days during which all medications and observation ceased; (b) 3 weeks during which the subjects received either placebo and attention or no placebo and no attention; (c) 3 weeks during which the precedures of (b) were reversed.

Inst (a) Pathologic activity: hourly recording by ward attendants using a 28-item checklist; (b) somnolence: half-hourly recording by ward attendants.

RC (a) Significant E/C reduction of pathologic activity and significantly increased somnolence. (b) The increased somnolence was not sufficient to account for the reduced pathologic activity. (c) A chlorpromazine carry-over effect of at least 3½ months was suggested by the data.

Com Analysis of the data apparently proceeded on the basis of each subject as his own control, and not on the basis of a drug versus concomitant placebo control. Therefore, no conclusions about the effect of chlorpromazine as compared to a concomitant placebo are possible. On the basis of the data gathered during the 3-week pre-experimental period, the experimenters conclude that pathologic activity scores were sufficiently stable to permit measurement and statistical testing of changes induced by drugs. Recomputation of their data presented in Table I indicates that this judgment was incorrect ($F = 3.77$, $df = 2/22$, Treatments × Subjects design). *T*-tests indicate that the measurements taken during the second week were significantly higher than the measurements taken during the first or the third weeks. This result poses no problems for the statistical evaluation

of the data secured from the later stages of the study. However, it does indicate that the results should be generalized to a population in flux, rather than a stabilized population, regarding pathologic activity.

Dean, E. F., and Buker, S.: Schizophrenia Treated With and Without Chlorpromazine, Rocky Mountain M. J. 55:47-50, 1958.

HI General.

Ss 18 female schizophrenics. Age: M = 37, R = 26 to 47. Hosp: M = 5.8, R = 3 to 12. Of the 18 subjects, 16 had previously received 100 to 200 mg. of chlorpromazine for 3 to 6 months without response. The 18 subjects were selected from 40 subjects interviewed, largely on the basis of lack of response to previous treatment.

Med Standard schedule for the first 5 weeks, increasing from 100 to 1,000 mg. Individual schedules for the next 10 weeks, with each subject receiving her maximum dose for at least 2 of the 10 weeks. The largest maximum dose was 3,000 mg., the smallest maximum dose was 2,000 mg., and the majority had a maximum dose of 2,400 mg. Total duration of 15 weeks.

Des Linear design. Pre- and post-evaluations. A total push program of work therapy, psychotherapy, and increased attention was instituted for the entire group.

Inst (a) Improvement rating (none or worse, improvement, basic improvement) independently by ward doctor, clinical psychologist, social worker, and activity therapy worker; (b) brief verbal IQ test (comprehension, vocabulary, similarities); (c) weight.

RC Significant E/C improvement on all measures.

Com A statistically significant E/C improvement was obtained on the clinical evaluation. There was no statistical evaluation of the IQ or weight measure (E/C IQ change = +7; E/C weight change = +5.8).

Feldman, P. E., Lacy, B. S., Walker, A. E., and Garrez, N. J.: A Controlled, Blind Study of Effects of Thorazine on Psychotic Behavior, Bull. Menninger Clin. 20:25-47, 1956.

HI General

Ss 22 males, mostly schizophrenics. Age: M = 45.6, R = 18 to 73, SD = 13.80. Hosp: M = 9.0, R = 0.25 to 29, SD = 8.29.

Med* Standard schedule (except for a few cases): 200 mg. for 5 weeks, 300 mg. for 2 weeks, 400 mg. for 5 weeks. Total duration of 12 weeks.

Des Linear design. Pre- and post-testing.

Inst (a) Improvement rating (none, slight, moderate, marked) based upon independent interviews by four psychiatrists; (b) Ferguson Rating Scale.

RC Significant E/C improvement on the clinical interviews.

Com When a two-tail test is utilized, there are no significant E/C differences. The experimenters present two chi square analyses on page 33, both of which were computed from the data presented in Chart No. 5. The second of these is presented in the RC section above. The first of these analyses ("using the clinical rating data. . ."), however, was not clear, and we have not been able to compute a chi square based on Chart No. 5 which yields a P value of 0.01.

Freeman, H., and Cline, H. S.: Effects of Chlorpromazine on Chronic Lobotomized Schizophrenic Patients, A.M.A. Arch. Neurol. & Psychiat. 76:500-507, 1956.

HI Threshold dosage of chlorpromazine.

Ss 20 male schizophrenics. Age: M = 37.3, R = 23 to 57. Hosp: M = 10.3, R = 4 to 27. All subjects had been lobotomized. Time since lobotomy: M = 7.8, R = 1 to 16.

Med* Standard schedule: 200 mg. for 4 weeks, 400 mg. for 2 weeks, 600 mg. for 2 weeks, 800 mg. for 3 weeks. Total duration of 11 weeks.

Des Linear design. Weekly evaluations. E and C subjects were matched primarily on the rating scores and secondarily according to age, duration of hospitalization, and years since lobotomy. Follow-up study for 4 weeks: E subjects received placebo and C subjects received no treatment.

Inst Modified Malamud Sands Rating Scale completed on the basis of a psychiatric interview.

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RC Significant E/C improvement on the total scale and on four items: responsiveness, socialization, perception, and thought processes. The results suggest a return to the base line within 4 weeks (follow-up study).

Com The primary interest was not tested since dosage level was confounded with time. There was no placebo control for the "return to the base line" analysis of the follow-up study. The greatest improvement occurred at the eighth week when 800 mg. was administered. The tests for E/C change were computed by comparing the sum of the scores for the 3 weeks before the 800 mg. dose was started with the sum of the scores after the 800 mg. was started.

Fromm, G. H., and Forsberg, I. A.: Controlled Study on the Value of Chlorpromazine in Allaying Anxiety, Dis. Nerv. System 17:16-19, 1956.

HI (a) General, (b) anxiety.

Ss 21 males, mostly psychotics. Age: 17 subjects under 40, four subjects over 40. Hosp: new admissions.

Med* Standard schedule for about 4 days: started at 200 mg. and increased by 100 mg. each day until the desired effect was obtained or a maximum of 500 mg. was reached. Individual maxima thereafter with most subjects on their maximum dose for 2 weeks. Total duration of 2 to 3 weeks.

Des Linear design. Pre- and post-evaluations. E and C subjects were roughly matched for anxiety, length of illness, psychosis versus no psychosis, and age.

Inst (a) MSRPP: the total morbidity measure, based upon psychiatrist's rating; (b) Anxiety: five-point rating based upon an interview by three staff members.

RC Significant E/C clinical improvement and reduction of anxiety.

Com Since the statistical evaluation was not presented, we recomputed the data. For the purpose of at least a superficial statistical evaluation, a 2×2 analysis of variance (E versus C and psychotic versus nonpsychotic) was computed for the MSRPP and for the anxiety scores. The criterion measures consisted of difference scores (pre-post). Since there was an uneven distribution of subjects in the four cells (7 of 12 psychotic subjects and 5 of 9 nonpsychotic subjects received chlorpromazine), the cells with 7 and 4 subjects were weighted by multiplying ΣX and ΣX^2 by 5/7 and 5/4, respectively. No significant F ratios were obtained on the MSRPP. On the anxiety scale, however, F ratios of 5.40 and 4.96 (df = 1/16) for E versus C and psychotic versus nonpsychotic, respectively, were significant, indicating that the E subjects showed a significantly greater reduction of anxiety than the C subjects and that the nonpsychotic subjects showed a significantly greater reduction of anxiety than the psychotic subjects regardless of which medication was received.

P. 17: "A few cases had to be taken off the project after only twelve to fourteen days of treatment due to lack of a favorable response and urgent need of more effective treatment. This appeared to be justified, as it has been our experience in using chlorpromazine that patients who are going to respond favorably to this drug when given orally show some definite improvement during the first 24 to 48 hours after the medication is started." This quotation, as well as the phrase in the medication section, ". . . until the desired effect was obtained," indicate that the expectations of the experimenters may have been reflected in the data. Further, if the expectation that definite improvement occurs within 48 hours after the start of medication is to be consistently applied, the experiment need only last 48 hours.

Gibbs, J. J., Wilkens, B., and Lauterbach, C. G.: A Controlled Clinical Psychiatric Study of the Drug Chlorpromazine, Am. J. Psychiat. 113:254-255, 1956.

Gibbs, J. J., Wilkens, B., and Lauterbach, C. G.: A Controlled Clinical Psychiatric Study of Chlorpromazine, J. Clin. & Exper. Psychopath. 18:269-283, 1957.

HI (a) Accessibility to psychotherapy, (b) threshold dosage.

Ss 39 subjects; 24 males (U. S. Army) and 15 females (civilian dependents); mostly neurotics. Age: M = 25.5, SD = 17.4. Hosp: new admissions.

Med Individual schedules for 6 weeks. Lower dosage group received a minimum of 75 mg. and

a maximum of 125 mg.; the higher dosage group received a minimum of 150 mg. and a maximum of 450 mg.

Des Linear design. Pre- and post-testing. Three groups were utilized: placebo, low dosage chlorpromazine, and moderate dosage chlorpromazine. All subjects received approximately 6 hours of psychotherapy.

Inst (a) Malamud Sands Rating Scale rated independently by two psychiatrists; (b) Wechsler-Bellevue Adult Intelligence Scale (WAIS) scored on the full scale, verbal, and performance; (c) MMPI: 13 measures.

RC No significant E/C differences.

Com Psychotherapy (either group or individual) was a constant for all subjects. Therefore the experiment was not designed to answer the major interest. A probable biasing factor was emphasized by the experimenters, namely, the psychiatrist conducting the psychotherapy was cognizant of the medication code. Four subjects developed side effects early in the study and were transferred to a different treatment group (presumably the placebo group). Such manipulation of subjects after the start of the experiment can also be considered as a biasing factor. Since the three treatment groups had not been directly compared on any of the measures, we computed chi squares (Table V) and analyses of variance (Table VI) comparing all three groups on each variable. There were no significant differences among the groups.

Gilgash, C. A.: Effects of Thorazine on Wechsler Scores of Adult Catatonic Schizophrenics, Psychol. Rep. 3:561-564, 1957.

HI Social, emotional, and intellectual functioning.

Ss 44 catatonic schizophrenics (the sex breakdown was not described). Age: M = 32, R = 18 to 44. Hosp: M = 6.3.

Med Constant schedule of 300 mg. for 30 days.

Des Linear design. Pre- and post-testing. E and C subjects were roughly matched on the basis of admission diagnosis, age, sex, and IQ.

Inst Wechsler-Bellevue Intelligence Scale: full scale, verbal, and performance.

RC Significant E/C improvement.

Com Since the only criterion measure was an estimate of intelligence, the experimenter generalizes to social and emotional changes by inference and observations. The use of defined social and emotional instruments would improve the generalization greatly. The *t*-test for full scale scores was an E/C comparison based upon postmedication scores only. Although it did not make any practical difference here, an E/C comparison utilizing change scores is preferable.

The verbal and performance changes were evaluated for each group separately. No E/C conclusions can be drawn from these evaluations, since the two groups were not directly compared and not enough data were presented to go beyond the conclusion that the E group showed a significant improvement while the C group did not show a significant improvement. There appears to be an error in either the computation or presentation of the E change scores on the full scale: The average change for the E group (N = 22) was +11.50; the average change for the 13 subjects with less than 5 years hospitalization was +13.1; the average change for the 9 subjects with more than 5 years hospitalization was +10.56. The discrepancy, though small, could be basic if it reflects a computational error.

Good, W. W., Sterling, M., and Holtzman, W. H.: Termination of Chlorpromazine With Schizophrenic Patients, Am. J. Psychiat. 115:443-448, 1958.

Mefferd, R. B., Jr., Labrosse, E. H., Gawienowski, A. M., and Williams, R. J.: Influence of Chlorpromazine on Certain Biochemical Variables of Chronic Male Schizophrenics, J. Nerv. & Ment. Dis. 127:167-179, 1958.

HI Withdrawal effects: general, intellectual, personality.

Ss 112 male schizophrenics. Age: M = 36.6, R = 22 to 50, SD = 6.5. Hosp: R = 2 months to several years. All subjects had been on continuous maintenance doses long enough to have stabilized to its action (34 to 514 days) and all had shown some improvement during treatment.

Med* Individual schedules for 6 months with a 200 mg. minimum and an 800 mg. maximum (86 per cent of the subjects received 400 mg.).

Des Crossover design. Variable testing schedule (see Inst). The total duration of 6 months was divided into two stages of 3 months each. Stage 1: 56 E subjects and 56 C subjects. Stage 2: One-half of each group was switched. Seven levels were constituted on the basis of previous length of continuous chlorpromazine treatment.

Inst (a) Modified MSRPP: independent ward behavior ratings by nurse and aide (pre-test and at 3-week intervals); interview ratings by ward psychiatrist based on interview and daily observations (pre-test and at the end of each stage); (b) Army Beta (pre-test and at the end of each stage); (c) Bender-Gestalt scored by a modified Pascal-Suttell system (pre-test and at the end of each stage); (d) Draw-a-Person scored for intellectual level (pre-test and at the end of each stage); (e) weight (during stage 2 only, at 12, 18, and 24 weeks). (Biochemical measures, not included in this summary, were also taken at these times.)

RC (a) No significant differences during stage 1. (b) During stage 2, the subjects who had continuously received placebo deteriorated significantly on the total morbidity measure of the MSRPP as compared to the other three groups and lost significantly more weight. (c) No significant differences among the seven levels (previous length of chlorpromazine treatment). (d) The experimenters suggest that periodic short-term withdrawal of chlorpromazine is a feasible treatment program.

Com Only three of the 11 MSRPP factors were analyzed: C (paranoid projection), D (activity level), and F (perceptual distortion). Although the experimenters (Mefferd and co-workers) state that a significant treatment × trial interaction was obtained on C and F, it is not clear which group or groups differed.

Grygier, Patricia, and Waters, M. A.: Chlorpromazine Used With an Intensive Occupational Therapy Program: A Controlled Study, A.M.A. Arch. Neurol. & Psychiat. 79:697-705, 1958 [British].

HI Effect of chlorpromazine as compared to the total therapeutic program.

Ss 24 female schizophrenics. Age: M = 50, SD = 10.7. Length of illness: M = 20, SD = 11.8.

Med* Constant schedule of 150 mg. for 6 months.

Des Linear design. Variable testing schedule (see Inst). Stage 1: 3 months of intensive OT. Stage 2: 3 months of usual routine. E and C subjects were roughly matched on age, duration of illness, intelligence, and aptitude for OT. The 24 subjects were taken from two separate replications.

Inst (a) Albany Behavior Rating Scale: independently by ward nurse and head occupational therapist (at the end of 1, 6, 12, and 24 weeks); (b) four-point OT improvement rating: various occupational therapists (post-test); (c) cognitive tests: information, vocabulary, and an adaptation of the Porteus Maze (pre- and post-tests).

RC (a) Significant E/C improvement on the ABRS during stage 1 and the 6-month period. (b) Duration of illness was the most important single prognostic factor.

Com The primary interest was not tested. When a two-tail test is used to test E/C changes on the ABRS, the stage 1 difference is significant, but the 6-month difference is not ($p = 0.10$). The analyses of various measures as prognostic factors did not include E/C comparisons.The experiment utilized two independent samples. It is difficult to evaluate this procedure. The experiments reported, and discussed, that the C subjects of the two samples behaved differently during stage 2. At the end of the experiments, the ABRS raters were questioned as to which group the various subjects had belonged. One of the raters was able to guess fairly accurately on the basis of a photosensitive reaction. The experimenters then attempted to control for the potential bias which may have been introduced into the ratings. Although the control procedure was admittedly crude, due to the small N, this is the only serious attempt to deal with the potential bias introduced by "side effects," even when individual medications are used.

Hall, R. A., and Dunlap, Dorothy J.: A Study of Chlorpromazine: Methodology and Results With Chronic Semi-disturbed Schizophrenics, J. Nerv. & Ment. Dis. 122:301-314, 1955.

HI (a) General, (b) problems of experimental design in double blind studies.

Ss 175 schizophrenics; 54 males and 121 females. Age: M app. = 44, R app. = 20 to 59. Hosp: M app. = 7, R app. = 1 to 9. All subjects with seizures were eliminated except those with onset after lobotomy [?].

Med Individual schedules for 2 months. Minimum = 75 mg., maximum = 750 mg., average dosage was probably between 350 and 400 mg. Intramuscular administration was used with resistant subjects.

Des Linear design. Variable testing schedule (see Inst).

Inst (a) Five-point ward observation scale: all ward personnel (daily); (b) Fergus Falls Behavior Rating Scale: ward charge (weekly); (c) psychiatric interviews scored on a five-point scale of general change (pre- and post-test); a post psychiatric interview also conducted by a psychologist; (d) Bender-Gestalt (pre- and post-test).

RC (a) Significant E/C improvement on the psychiatric interviews, the paranoid subgroup showing the greatest response. (b) Significant E/C reduction in delusions. (c) The greater was the initial tension, the greater was the improvement (positive correlation between initial tension and improvement).

Com The experimenters concluded that the ward attendants were not "blind" and that the psychiatrists and psychologist were neither completely "blind" nor completely "unblind." The significant E/C reduction in delusions utilized the frequency of occurrence during treatment as the per cent of frequency during the pretreatment period. Interpretation of ratio scores may be limited by the fact that the scores become more unstable as the absolute frequency expressed in the denominator (pretreatment scores) becomes smaller. Since the pretreatment scores were not presented, this limitation cannot be evaluated.

Heilizer, F.: The Effects of Chlorpromazine Upon Psychomotor and Psychiatric Behavior of Chronic Schizophrenic Patients, J. Nerv. & Ment. Dis. 128:358-364, 1959.

Planansky, K., and Heilizer, F.: Weight Changes in Relation to the Characteristics of Patients on Chlorpromazine, J. Clin. & Exper. Psychopath. 20:53-57, 1959.

HI (a) General, (b) specific, (c) premedication behavior, (d) measures sensitive to schizophrenia, (e) withdrawal effects.

Ss 64 male schizophrenics. Age: M = 45.5, R = 26 to 69, SD = 9.0. Hosp: M = 14.2, R = 3 to 32, SD = 7.0.

Med Constant schedule of 300 mg. for 3 months. Six-week follow-up during which all subjects received placebo.

Des Linear design (partial crossover for the follow-up). Evaluations: (a) Lorr: pre- and post-tests, 6-week follow-up; (b) weight: before, weekly for 2 months, and a single weighing at the end of 3 months; (c) reaction time, finger dexterity, Bender-Gestalt: before, 2 weeks, 8 weeks, and 6 week follow-up.

Inst (a) Lorr MSRPP Interview Scale: by the experimenter (N = 48, withdrawal N = 38); (b) weight (N = 59); (c) lift and jump reation time: speed and variability (N = 44, withdrawal N = 32); (d) finger dexterity (N = 44, withdrawal N = 32); (e) Bender-Gestalt (N = 44, withdrawal N = 32).

RC (a) No significant E/C difference in general morbidity (Lorr). (b) Significant E/C improvement: weight, variability jump reaction time, F factor of the Lorr scale (perceptual distortion). (c) Significant E/C decrease in alertness (A factor of the Lorr scale: retarded depression versus manic excitement). (d) Significant E/C initial score effect on variability jump reaction time. (e) Changes in weight, variability jump reaction time, and the A factor of the Lorr scale were significantly intercorrelated for the E subjects. (f) Significant E/C increase in alertness (A factor of the Lorr scale) upon withdrawal of chlorpromazine.

Com The withdrawal effect was obtained with an atypical sample as compared to the original sample. A significant E/C improvement in speed of jump reaction time was erroneously reported in Planansky and Heilizer [author's error].

Hine, F. R.: Chlorpromazine in Schizophrenic Withdrawal and in the Withdrawn Schizophrenic, J. Nerv. & Ment. Dis. 127:220-227, 1958.

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HI (a) General, (b) withdrawal, (c) prognostic significance of the intensity of withdrawal.
Ss 21 female schizophrenics. Age: R = 30 to 50. Hosp: minimum of 5 years.
Med* Individual schedules for 20 weeks. Minimum = 150 mg., maximum = 750 mg. The dosage was increased from 150 mg. until symptomatic or mild side effects were noted or until a level of 750 mg. was reached.
Des Linear design. Ratings weekly or at 5-week intervals. E and C subjects matched on initial withdrawal.
Inst (a) Direct (subjective) judgment: independent ratings of withdrawal by the ward nurse, a research assistant, and the experimenter (5-week intervals); (b) Southeast Louisiana Hospital Behavior Rating Scale: withdrawal items were utilized after the scale had been rated by attendants, the ward nurse, and the experimenter (weekly); (c) general hospital status: utilized as a measure of psychiatric improvement (e.g., acquisition of ground privileges).
RC (a) Significant E/C improvement in general hospital status. (b) No significant E/C differences on withdrawal and no significant relationship between initial withdrawal and psychiatric improvement.

Mefferd, R. B., Jr., Labrosse, E. H., Gawienowski, A. M., and Williams, R. J.: Influence of Chlorpromazine on Certain Biochemical Variables of Chronic Male Schizophrenics, J. Nerv. & Ment. Dis. 127:167-179, 1958. See: Good, Sterling, and Holtzman.

Merry, J., Pargiter, R. A., and Munro, H.: Chlorpromazine and Chronic Neurotic Tension, Am. J. Psychiat. 113:988-990, 1957 [British].
HI Chronic neurotic tension.
Ss 21 male neurotics. Age: not mentioned. Hosp: new admissions. Two admitting psychiatrists agreed that each subject was suffering from chronic neurotic tension.
Med Individual schedules for 4 weeks. Minimum = 150 mg., maximum = 300 mg.
Des Linear design. Pre- and post-testing.
Inst (a) 25 additions: total time; (b) three write-a-story tests from the MAPS: latency and speed; (c) clinical assessment.
RC No significant E/C differences.
Com Due to various difficulties, N = 16 for the psychologic tests (additions and stories), with 8 in each group.

Mitchell, P. H.: Chlorpromazine in the Treatment of the Chronic Disturbed Schizophrenic Patient, J. Ment. Sc. 102:151-154, 1956 [British
HI Aggressive outbursts.
Ss 36 male schizophrenics. Age: M = 35, R = 29 to 50. Length of illness: minimum of 10 years.
Med Constant schedule of 150 mg. for 6 weeks (experiment 1); constant schedule of 300 mg. for 10 weeks (experiment 2).
Des Linear design. Daily (continuous) observations. Experiment 1: 6-week preliminary recording period followed by 6 weeks of medication; Experiment 2: 12-week rest period, 2-week preliminary recording period, 10 weeks of medication.
Inst (a) Aggressive outbursts: four-point rating of intensity and length by the nursing staff; (b) weight.
RC (a) No significant E/C change in aggressive outbursts. (b) Significant E/C weight increase.
Com No statistical evaluation was presented nor was a specific statistic mentioned, although the experimenter refers to "significant" and "statistically." Subjects were assigned to E or C on the basis of the first letter of their last name (A-L in one group and M-Z in the other group). This is a random procedure only if there is no correlation between last names and the occurrence of schizophrenia or either of the criterion measures. Even if this procedure is a true randomization, the use of last names in this manner provides a simple key to a medication code.

The experimenter makes an excellent point when he states, "Apart from the giving of tablets, the normal ward routine remained completely unchanged throughout." [p. 152.]

"To have attempted to separate the patients into different categories or record groups of elaborate symptoms, would have been to have destroyed the whole object of the experiment, which was to record the effects of the drug in a group of patients in which all other factors remained unchanged." [p. 153.]

Newbold, H. L., and Steed, W. D.: The Use of Chlorpromazine in Psychotherapy, J. Nerv. & Ment. Dis. 123:270-274, 1956.
This study is not being summarized, although it meets the formal criterion, because of the small sample (N = 4).

Planansky, K., and Heilizer, F.: Weight Changes in Relation to the Characteristics of Patients on Chlorpromazine, J. Clin. & Exper. Psychopath. 20:53-57, 1959. See: Heilizer.

Pleasure, H.: Chlorpromazine (Thorazine) for Mental Illness in the Presence of Pulmonary Tuberculosis, Psychiat. Quart. 30:23-30, 1956.

HI General.

Ss 57 subjects; 27 males and 30 females; mostly schizophrenics. Age: not mentioned. Hosp: not mentioned. All subjects had active tuberculosis and were receiving TB drugs.

Med Individual schedules for 4 months. Minimum = 100 mg., maximum = 1,800 mg. Nearly all subjects received at least 600 mg. at some time during the 4 months; about 1/3 received 900 mg. or more during this period.

Des Linear design. Time of evaluations not described.

Inst (a) Psychologic evaluation; (b) weight.

RC Significant E/C psychologic improvement and weight gain.

Com Neither the psychologic evaluation nor the statistical treatment (if any) is described. It appears likely, however, that both E/C changes are statistically significant. (a) A chi square computed from the experimenter's description of E/C improvement was significant (chi square = 6.56, df = 1). (b) From our experience with weight changes in schizophrenic patients, an E/C weight gain of 7.8 lbs. for a total sample of 55 subjects (2 subjects died during the experiment) is likely to be statistically significant.

Porteus, S. D.: Specific Behavior Changes Following Chlorpromazine, J. Consult. Psychol. 21:257-263, 1957 [I].

HI General.

Ss 100 males, mostly schizophrenics. Age: R = about 25 to over 80. Hosp: R = 2 to 57.

Med Constant schedule of 300 mg. for 18 weeks.

Des Linear design. Ratings at 3-week intervals.

Inst Ward behavior rating scale consisting of 11 traits was completed by two aides.

RC Significant E/C improvement on all traits except asocialization and compulsive behavior.

Com The E subjects and the C subjects were selected from two different wards, with no attempt to control or assess interward differences. Thus, although this study formally meets the criterion of a concomitant placebo control group, the sampling procedure renders it, in effect, outside the limits of this review. No statistical analyses were presented or mentioned. The various traits were evaluated by inspecting graphs for the E group only (the graphs for the C group were not presented or described). Total scale scores were presented for both groups but were not evaluated statistically. A chi square analysis would be significant, indicating a significant E/C improvement. However, there was apparently a computational error in the data for the C group: Since N = 50, all percentages must be multiples of two; this was not the case for the C-group data in Table I.

Porteus, S. D.: Maze Test Reactions After Chlorpromazine, J. Consult. Psychol. 21:15-21, 1957 [II].

Porteus, S. D., and Barclay, J. E.: A Further Note on Chlorpromazine: Maze Reactions, J. Consult. Psychol. 21:297-299, 1957.

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HI Porteus maze.
Ss 60 psychotics; minimum of 7 females. Age: not mentioned. Hosp: R = 3 to 57.
Med Constant schedule of 300 mg. (see Com) for from 6 weeks to 6 months.
Des Linear design. Pre- and post-testing.
Inst Porteus maze.
RC Significant E/C deterioration of about 2 years.
Com An additional description of the two articles is necessary in order to evaluate the data. There was some subject overlapping between Porteus I, on the one hand, and Porteus II and Porteus and Barclay, on the other. Thirteen E subjects were testable on the Porteus Maze of the 50 subjects reported in Porteus I. (No data were presented on how many C subjects were testable.) "Later, two male and seven female cases were added to the group, two of the women having had larger dosages for a shorter time, while five had had the same dosage but for a period of six weeks instead of four months." [Porteus II, p. 15.] These 22 E subjects provide the data for the preliminary report (Porteus II). Further data was provided by Porteus and Barclay who reported the data of 60 subjects: 35 E subjects and 25 C subjects. No description was given of how the additional 13 E subjects or any of the C subjects were selected. The constant schedule of 300 mg. reported in Porteus and Barclay was not consistent with the report in Porteus II. No reasons were given for a range of medication periods of from 6 weeks to 6 months.

There are several limitations to this study in addition to the selection of E subjects and C subjects from two different wards. (a) In Porteus II it was reported that the premedication testing of the original 13 E subjects was done by a graduate student and the postmedication testing was done by Porteus. The occurrence of a decrement for these subjects, then, may simply reflect some difference in experimenters. (b) The practice of adding subjects according to varying and not too well-specified criteria is not likely to produce reliable data. In an attempt to check this possibility, we recomputed the data presented in Table 2 of Porteus II. The only identifying characteristic of the 22 E subjects was the sex of the subject. All 7 females were added to the original group of 13, while 13 of the 15 male subjects were part of the original study (Porteus I). A Kruskal-Wallis nonparametric analysis of variance indicated that the female subjects showed a significantly greater deterioration than did the male subjects ($H = 5.96$, $df = 1$). The mean change score for the total group of 22 E subjects was -2.07; for the 15 male E subjects it was -1.07; for the 7 female E subjects it was -4.21. Although this result cannot be meaningfully interpreted due to the several confounded variables, it does lend added emphasis to the limitations that should be placed upon interpretations of these data.

Rathod, N., and Rees, L.: A Controlled Study of the Prognostic Significance of Autonomic Responses in the Chlorpromazine Treatment of Disturbed Psychotic Patients, J. Ment. Sc. 104:705-712, 1958 [British].

HI General.
Ss 27 female psychotics (16 affective and 11 schizophrenic). Age: not mentioned. Hosp: probably new admissions.
Med Individual schedules for two stages of 8 days each. Minimum = 150 mg., maximum = 250 mg. (for almost all patients). Intramuscular administration for the first 4 days.
Des Crossover design. Daily observations and pre- and post-testing for each stage. Stage 1: E group and C group for 8 days. Stage 2: medication was switched for 8 days.
Inst (a) Daily nursing notes; (b) clinical progress notes by physician; (c) fourteen-item rating scale by physician. The data presented in the paper were based upon a composite of these three measures.
RC Significant E/C improvement.
Com We do not believe that this kind of crossover design (where the medication is switched for two groups and the data for the two stages are combined) provides usable data. There are two sources for this judgment. (a) A distinction between drug effect and withdrawal effect is usually made in clinical practice. Each effect is important in its own right as an integral part of the therapy process. A design such as used here combines the two effects

and does not allow for an independent evaluation of either effect. (b) A 2 × 2 Latin Square design allows (or requires, depending upon one's attitude) an analysis of the interaction effect. If a significant interaction obtains, the simple effects are to be analyzed, i.e., the effect of medication at each stage. A failure to analyze for the interaction effect implies that it is either not significant or not important. The former implication may be dangerous and is unnecessary in view of the empirical answer which is easily available, while the latter implication is not consistent with prevailing clinical practice and attitudes. The position outlined above receives additional import from such a report as the following: "The improvement was only temporary in 50 per cent, being followed by relapse despite continued medication." [p. 710.] The statistical analyses do not appear to have considered that nonindependent frequencies were used.

Rees, W. L., and Lambert, C.: The Value and Limitations of Chlorpromazine in the Treatment of Anxiety States, J. Ment. Sc. 101:834-840, 1955 [British].

HI Anxiety.

Ss 150 outpatients in anxiety states; 49 males, 101 females. Age: M = 39, R = 16 to 75.

Med Standard schedule for the first 2 days of each stage: 25 mg. the first day, 50 mg. the second day. Constant schedule of 75 mg. for the next 14 days of each stage. Total duration of 16 days for each stage.

Des Crossover design. Evaluations before and at the end of each stage. Stage 1: E group and C group for 16 days. Stage 2: medication was switched for 8 days.

Inst (a) Seven-point scale of general clinical change was derived from (b) item sheet with information about the social data, family and personal history, personality, clinical state, and symptomatology. Particular attention was paid to various aspects of emotional tension, and a composite rating of total tension was made for each subject.

RC Significant E/C improvement.

Com The only E/C comparison utilized the general clinical change score. The same objections apply to this crossover design as apply to the study by Rathod and Rees. It appears that the *t*-test for proportions is not appropriate, i.e., it assumes independent groups.

Seager, C. P.: Chlorpromazine in Treatment of Elderly Psychotic Women, Brit. M. J. 1:882-885, 1955 [British].

HI General.

Ss 46 female psychotics, mostly organics, about 25 per cent schizophrenics. Age: M app. = 72, R = 58 to 87. Hosp: not mentioned.

Med Constant schedule for 22 subjects: 150 mg. intramuscularly for 1 week, 150 mg. orally for 3 weeks. Standard schedule for 24 subjects: 75 mg. for 3 days, 150 mg. for 10 days, 225 mg. for 2 weeks. Total duration of 4 weeks.

Des Linear design. Post-evaluation.

Inst Rating of improvement (none, some, definite, marked).

RC Significant E/C improvement.

Com This study was actually a crossover design. Since the data were presented for stage 1, however, the study was summarized in terms of a linear (stage 1) design except for RC, which is the experimenter's. We analyzed the frequency data for the linear design. A significant E/C improvement resulted for the total group (chi square = 12.66, df = 1) and for the subjects who were on a constant medication schedule with initial intramuscular administration (chi square = 14.85, df = 1), but not for the subjects who were on a standard schedule with oral administration throughout (chi square = 0.67, df = 1). When the chi square and df for the two subgroups are summed, and the chi square and df for the total group is subtracted from this sum, the result, although interesting, is not significant (chi square = 2.86, df = 1).

It is not clear why intramuscular administration was used initially with some subjects with a constant medication schedule when other subjects received oral medication throughout with a standard medication schedule.

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Sommerness, M. D., Lucero, R. J., Hamlon, J. S., and Mahowald, A. M.: Chlorpromazine: A Controlled Study With Highly Disturbed Patients, Dis. Nerv. System 18:16-20, 1957.

HI (a) Tranquilization, (b) social behavior.

Ss 66 females, mostly schizophrenics. Age: M = 45.5. Hosp: M = 17.

Med* Individual schedules for 12 weeks. Minimum = 100 mg., maximum = 1,200 mg. The final dosage varied between 300 and 1,200 mg. with an average of 633 mg.

Des Linear design. Weekly ratings. E and C subjects were matched on the basis of premedication behavior ratings. Four-week postmedication period.

Inst (a) Fergus Falls Behavior Rating Scale: by two psychiatric aides; (b) records of the frequency of ECT, seclusion, sedation; (c) weight.

RC (a) Significant E/C improvement on the rating scale. The E group improved immediately, the E/C difference becoming significant at 4 weeks and continuing through the 4-week postmedication period. (b) Significant E/C reduction in ECT, seclusion, sedation. (c) No significant E/C change in weight.

Com Neither interest was tested. The data are pertinent only to a general hypothesis. The subjects were placed on one ward prior to the onset of the experiment. If the chi square mentioned by the experimenters was computed from Table 1 (ECT, seclusion, sedation), it is not valid because of nonindependent frequencies. Inspection of Graph 1 seems to indicate a sudden E/C improvement on the rating scale between the third and fourth week of medication.

Tenenblatt, Sarah S., and Spagno, A.: A Controlled Study of Chlorpromazine Therapy in Chronic Psychotic Patients, J. Clin. & Exper. Psychopath. 17:81-92, 1956.

HI (a) General, (b) effect of length of medication.

Ss 100 females, mostly schizophrenics. Age: M = 35.6, R = 8 to 57, SD = 8.75. Duration of illness: M = 5.46, R = 1 to 24, SD = 5.01.

Med Standard schedule for the first 3 days: 50 mg. the first day, 100 mg. the second day, 150 mg. the third day. Individual schedules thereafter: 150 or 300 mg. the fourth day with a 50 or 100 mg. increase every 5 days until maximum improvement was obtained. Highest maximum = 900 mg., lowest maximum = 300 mg. Total duration varied from 16 to 116 days. Intramuscular administration was used for the first 3 days.

Des Linear design. Post-evaluation based on continuous observation. E and C subjects were roughly matched on age, duration of illness, diagnosis, and behavior. "The duration of therapy was varied from group to group [?] in order to determine the optimum time." [p. 85].

Inst Six-point rating of change: a consensus of the ratings by "all personnel involved in this project."

RC Significant E/C improvement. For the E group: age, duration of illness, and previous therapy bear no relation to amount of improvement.

Com The subjects were transferred to two wards prior to the onset of the experiment. There was no description of the procedure used for determining the duration of medication. The procedure of increasing the dosage level until "maximum improvement" was obtained may have been involved on an a posteriori basis. The experimenters state: "The most significant result of the chlorpromazine therapy was noted in the difference of response on the two wards. This was attributed to the personalities of the nurses and attendants, since their enthusiasm for the drug varied in intensity." [p. 87.]

There were some discrepancies between what the experimenters intended and what occurred. For example, they write: "The entire project was rigidly controlled to prevent extraneous factors such as psychotherapy, additional attention, and increased privileges from obscuring the effect of the drug." [p. 91.] The study, however, appeared to involve more added attention, above and beyond usual hospital routine, than any other in this bibliography, e.g., subjects were transferred to new wards, individual dosages were prescribed daily, subjects were encouraged to rest in bed, frequent meetings were held with ward personnel and relatives of subjects to further understanding of the study and to allay anxiety, multitudinous recordings were made, etc. Further, a statement like the

following constitutes more of a denial of a problem than an attempt to work it through: "The ward personnel was cautioned against giving the patients extra attention, as was done in studies conducted in other parts of the hospital. This eliminated the psychotherapeutic factor which has frequently been considered the real reason for the efficacy of the drug." [p. 84.] Although these discrepancies were highlighted in this study, they are common occurrences which are usually overlooked due to a restricted reporting of aims and procedures. It probably happens more often than not that a drug study involves a drastic change in the routine of patients and ward personnel. The changes occur in connection with the study and, upon its completion, the ward gratefully subsides to a "normal" routine. The implications of such a procedure for drug research would seem to merit more serious consideration than is usually the case.

We computed random analyses of variance from the data presented in Table 3 (for the E group only) in an attempt to evaluate the relationships between the independent variable (general change) and the dependent variables (e.g., age, duration of treatment, etc.). Subjects with a change rating of 1, 2, or 3 were grouped together and subjects with a rating of 5 or 6 were grouped together, thus making three groups: I. Improved, N = 20; II. slightly improved, N = 18; III. not improved, N = 12. Analyses were done for age, duration of illness, days of treatment, maximum dose, and average dose. The only significant effect (F = 3.46, df = 2/47) was found on the age variable: group II (slightly improved) was significantly younger than group III (not improved).

Tourlentes, T. T., Hunsicker, A. L., and Hurd, D. E.: Chlorpromazine and Communication Processes, A.M.A. Arch. Neurol. & Psychiat. 79:468-473, 1958.

HI Communication processes.

Ss 34 female schizophrenics. Age: M = 61.2, R = 45 to 74. Hosp: M = 18.6, R = 4 to 39.

Med Constant schedule of 200 mg. for two stages of 6 weeks each.

Des Partial crossover design. Testing before and at the end of each stage. Stage 1: group A received chlorpromazine, groups B and C received placebo. Stage 2: group B received chlorpromazine, groups A and C received placebo.

Inst (a) Ten psychologic tests scored for 17 categories; (b) psychiatric interviews scored for eight categories; (c) sociometric evaluation scored for social interaction (paper and pencil test); (d) cinematographic record of random behavior during a 10-minute interval.

RC No significant E/C improvement in communication processes.

Com There was no indication as to which of the measures corresponded to the experimenters' concept of communication processes. The subjects were placed on one ward prior to the onset of the experiment. The same objections apply to this crossover design as were mentioned earlier. No direct comparisons among the three groups were made at any time. A total of 153 *t*-tests and chi squares (our best estimate) were done comparing pre- versus post-test measures for each of two stages and for each of the three groups. (Seventeen tests were significant.)

Trethowan, W. H., and Scott, P. A. L.: Chlorpromazine in Obsessive-Compulsive and Allied Disorders, Lancet 1:781-785, 1955 [British].

HI General.

Ss 59 neurotics with obsessive-compulsive features; 30 males and 29 females. Age: M = 35, R = 20 to 57. Hosp: outpatients.

Med Individual-Standard schedules: 50-75 mg. the first week, 100 mg. the second week, 150-200 mg. the third and subsequent weeks. Chlorpromazine medication schedules were from 2 to 13 weeks with a total duration of from 7 to 18 weeks (see Des).

Des Crossover design. Pre- and post-evaluations and weekly recordings. Four groups: (a) E for 4 to 5 weeks, C for 1 to 3 weeks, E for 2 to 13 weeks; (b) E for 4 to 6 weeks, C for 1 to 2 weeks, no treatment for 1 week: (c) C for 2 to 3 weeks, E for 4 to 6 weeks, C for 1 to 3 weeks; (d) C for 2 to 3 weeks, E for 4 to 7 weeks, no treatment for 1 week.

Inst (a) Degree of disability: pre- and post-test ratings derived from (b) weekly psychiatric interview and (c) weekly symptom check-list by psychiatrist; (d) weight.

RC Subjects in whom anxiety and tension were prominent did best. Little relief of obsessive-compulsive symptoms, apart from aggressive urges and hypochondrial ideas, was obtained. In those who responded, sudden withdrawal of chlorpromazine produced a relapse. After this some did not respond when chlorpromazine was again given.

Com The same objections apply to this crossover design as were mentioned earlier. These objections are compounded by a complexity of design which defies analysis and discourages generalizations.

Vaughan, G. F., Leiberman, D. M., and Cook, L. C.: Chlorpromazine in Psychiatry, Lancet 1:1083-1087, 1955 [British].

HI General.

Ss 48 females; about 50 per cent schizophrenics and 40 per cent in affective states. Age: M = 43. Hosp: M = 9.6.

Med Individual schedules for an unspecified duration. Minimum = 75 mg., maximum = 450 mg., most subjects received 150-200 mg. Intramuscular administration was used with some subjects for the first 4 days.

Des Linear design. Evaluation periods not indicated.

Inst Four-point improvement rating.

RC Significant E/C improvement.

Com The study was sketchily presented. The study summarized here corresponds to group B in the article. The study which corresponds to group A was not summarized here because it does not meet the criteria for inclusion.

Whitehead, W. A., and Thune, L. E.: The Effects of Chlorpromazine on Learning in Chronic Psychotics, J. Consult. Psychol. 22:379-383, 1958.

HI (a) Learning, (b) verbalized social adaptation.

Ss 52 males, mostly schizophrenics. Age: M = 38.5, R = 23 to 63. Hosp: M = 8.35, R = 2 to 26.

Med Individual-Standard schedules for 2 months: "Dosage was gradually increased to about 800 mg. per day, usually over a period of about 35 days, and then gradually decreased until evaluation, at which time 36 Ss were receiving a minimum of 300 mg., and 16 Ss were receiving 200 mg./day." [p. 379].

Des Linear design. Post-testing.

Inst (a) Pursuit rotor; (b) verbal learning: eight-item serial questionnaire; (c) problem solving; (d) Verbalized Social Adaptation Questionnaire.

RC (a) Significant E/C improvement in cooperation (testability); (b) significant E/C improvement on verbalized social adaptation. (c) No other significant E/C differences.

Com The medication schedule is unusual. Pre- and post-testing is to be preferred to a post-testing for the generalizations which were made.

Winter, W. D., and Frederickson, W. K.: The Short-term Effects of Chlorpromazine on Psychiatric Patients, J. Consult. Psychol. 20:431-434, 1956.

HI (a) Chlorpromazine will not produce personality trait changes as measured by the MMPI. (b) Chlorpromazine will produce an improvement in overt ward behavior, related to a decrease in subjective anxiety. (c) Tests involving visual-motor coordination will be contaminated by the physical side effects of chlorpromazine.

Ss 59 females; diagnoses not specified. Age: M = 33.5, R = 18 to 45. Hosp: new admissions.

Med Constant schedule of 200 mg. for 1 week.

Des Linear design. Pre- and post-testing.

Inst (a) Gardner Behavior Chart (N = 42): ward ratings by nurse; (b) Bender-Gestalt (N = 32): scored by a modified Pascal-Suttell system; (c) MMPI (N = 22).

RC No significant E/C differences.

Com Upon analysis of the data, a significant E/C difference was found on several MMPI scales for the premedication testing. Therefore, the E subjects and C subjects were matched on the basis of their premedication scores on each measure [?]. The following statement by

the experimenters does not seem to be justified on the basis of their analyses, although it might derive some support from a matched-pairs analysis of the data: "Our conclusions are that, in general, acutely disturbed patients tend to improve after a few days of hospitalization and that chlorpromazine speeds behavioral adjustment to ward routine, but that it causes some disruption of coordination, especially during the so-called 'turmoil phase' at the beginning of treatment. Evaluation of psychological tests involving visual-motor coordination, such as the Bender-Gestalt, should, therefore, take into account the effects of concurrent drug therapy." [p. 434]. Neither "subjective anxiety" (second hypothesis) nor "physical side effects" (third hypothesis) were defined or utilized in the article.

SECTION 2

Daston, P. G.: Effects of Two Phenothiazine Drugs on Concentrative Attention Span of Chronic Schizophrenics, J. Clin. Psychol. 15:106-109, 1959.

HI Concentrative attention span.
Ss 13 male schizophrenics. Age: maximum of 50. Hosp: minimum of 2.
Med* Constant schedule of 400 mg. for 3 months.
Des Linear design. Pre- and post-evaluations.
Inst Wechsler Memory Scale: two subtests (memory paragraph and paired associates).
RC Significant E/C improvement on paired associates.
Com This study actually used two additional groups (promazine and phenobarbital) and a crossover design of three stages. The study was summarized here as if it consisted only of a placebo and a chlorpromazine group with a linear design, with the exception of the RC section, which presents the experimenter's results. No significant E/C improvement was found when the data were recomputed for the first 3 months.

Denber, H. C. B.: Chlorpromazine-diethazine in the Treatment of Depression, Dis. Nerv. System 18:76-79, 1957.

HI General.
Ss 20 depressed psychotics, approximately a two-to-one ratio of males to females. Age: R = 17 to 70. Hosp: new admissions.
Med Constant schedule for from 16 to 160 days. One E subject received 150 mg., 9 E subjects received 300 mg.
Des Linear design. Post-evaluation.
Inst Four-point improvement rating: jointly by the experimenter, chief of service, treatment nurse, ward nurse; probably based, at least in part, upon daily ward notes by a special nurse.
RC No significant E/C improvement.
Com There was no description of the procedures used for determining the duration of medication.

Fleming, B. G., and Currie, J. D. C.: Investigation of a New Compound, B. W. 203, and of Chlorpromazine in the Treatment of Psychosis, J. Ment. Sc. 104:749-757, 1958. [British].

A crossover design was used and analyzed as a whole. Since the data for the first stage was not presented separately, this study does not provide usable data for our purposes.

Freeman, H., Arnold, A. L., and Cline, H. S.: Effects of Chlorpromazine and Reserpine in Chronic Schizophrenic Patients, Dis. Nerv. System 17:213-219, 1956.

The chlorpromazine versus placebo portion of this study is the same as Freeman and Cline in Section 1.

Gardner, M. J., Hawkins, H. M., Judah, L. N., and Murphree, O. D.: Objective Measurement of Psychiatric Changes Produced by Chlorpromazine and Reserpine in Chronic Schizophrenia, Psychiat. Res. Rep. 1:77-83, 1955.

HI General.

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Ss 19 male schizophrenics. Age: M app. = 29. Duration of illness: M app. = 8.

Med Standard schedule for 5½ weeks, increasing from 100 to 500 mg.; constant schedule of 500 mg. for 8 weeks; 2-week withdrawal period. Total duration of 15 to 16 weeks.

Des Linear design. Pre- and post-testing and testing before, during, and afterward on the MSRPP. Subjects were matched on the basis of the Lorr Total Morbidity Score.

Inst (a) Lorr scale (MSRPP); (b) Porteus Maze; (c) four Wechlser subtests: arithmetic, similarities, vocabulary, picture completion; (d) Graham-Kendall Memory for Designs; (e) Rorschach: total number of responses; (f) psychologic test performance: defined as a combination of the Lorr ward behavior scale, Wechsler vocabulary subtest, and Wechsler picture completion subtest; (g) clinical response: improved, partially improved, not improved.

RC Significant over-all E/C improvement.

Com No rationale was given for the combination of measures which form the psychologic test performance measure. If it was an a posteriori grouping, an evaluation in probability terms is invalidated. We computed Fisher exact chi squares from the frequency data presented in the text and tables. The clinical response and the resistive isolation pattern of the Lorr Scale were the only measures to demonstrate a significant E/C improvement.

Hollister, L. E., Jones, K. P., Brownfield, B., and Johnson, F.: Chlorpromazine Alone and With Reserpine, California Med. 83:218-221, 1955.

Hollister, L. E., Traub, L., and Beckman, W. G.: Psychiatric Use of Reserpine and Chlorpromazine: Results of Double-blind Studies, *in* Kline, N. S., editor: Psychopharmacology, Washington, D. C., 1956, Pub. No. 42, A.A.A.S., pp. 65-74.

HI General.

Ss 42 males, mostly schizophrenics. Age: M app. = 34, R = 18 to 77. Duration of illness: M app. = 9, R = 6 months to 35 years. Some of the subjects had undergone lobotomy.

Med Intramuscular administration of 150 mg. for the first 3 or 4 days. Constant schedule of 100 or 400 mg. for 10 days. Total duration of 2 weeks.

Des Linear design. Post-evaluation. Four groups: E, 100 mg., N = 14; E, 400 mg., N = 10; C, 100 mg., N = 12; C, 400 mg., N = 6.

Inst Judgment by ward psychiatrist: worse, unimproved, improved.

RC Significant E/C improvement.

Com We computed Fisher exact chi squares from the frequency data presented. A significant E/C improvement resulted for the total group as well as for the 100 mg. group, but not for the 400 mg. group.

The subjects were transferred to the medical ward for administration of the drug (probably for the first week).

Kornetsky, C., and Humphries, Ogretta: Relationship Between Effects of a Number of Centrally Acting Drugs and Personality, A.M.A. Arch. Neurol. & Psychiat. 77:325-327, 1957.

Kornetsky, C., Humphries, Ogretta, and Evarts, E. V.: Comparison of Psychological Effects of Certain Centrally Acting Drugs in Man, A.M.A. Arch. Neurol. & Psychiat. 77:318-324, 1957.

Primac, D. W., Mirsky, A. F., and Rosvold, H. E.: Effects of Centrally Acting Drugs on Two Tests of Brain Damage, A.M.A. Arch. Neurol. & Psychiat. 77:328-332, 1957.

HI (a) General, (b) drug × subject interaction.

Ss 10 normals; 6 males and 4 females. Age: M = 20.5, R = 18 to 23.

Med* Single (acute) administration of 200 mg. and 400 mg. for 4 subjects and 100 mg. and 200 mg. for 6 subjects. (The dosage was reduced owing to the severity of postural hypotension at the higher dosage level.) One administration per day with a minimum of 1 day between successive administrations.

Des Crossover design. Variable testing schedule (see Inst).

Inst Pre- and post-experiment: (a) Speed of addition (three digits); (b) speed of addition (nine digits); (c) modified digit symbol test; (d) speed of copying numbers; (e) pursuit rotor; (f) tachistoscopic visual discrimination; (g) tactual threshold determination. (h) symptom

questionnaire: 30, 90, 150, and 210 minutes after medication. Pre-experiment: (i) MMPI: Hy, Hs, D, and Pt scales. Post-experiment: (j) Wisconsin card sorting test (WCST); (k) continuous performance test (CPT): four measures. Tests (a) through (g): the scores were expressed as a per cent of two control scores, and then an over-all mean per cent score for all tests was obtained (the objective test score).

RC (a) Significant E/C decrement on digit symbol and pursuit rotor (only computed for the 200 mg. dose). (b) Significant over-all [tests (a) to (g)] E/C decrement at all three dosages. (c) Significant 400 mg./200 mg. decrement on speed of addition (three and nine digits), digit symbol, pursuit rotor, visual discrimination, and tactual threshold. (d) Significant 200 mg./100 mg. decrement on digit symbol. (e) Significant E/C increase in symptoms for the 400 mg. dose. (f) No significant correlation between the objective test scores and the symptom questionnaire under chlorpromazine medication (only computed for the 200 mg. dose). (g) Significant rank order correlation between the Pt scale of the MMPI and increase on the symptom questionnaire (rho = 0.73). (h) No significant correlations between the other MMPI scales and increase on the symptom questionnaire or between any of the MMPI scales and change on the objective test score (only computed for the 200 mg. dose). (i) No significant E/C difference on the WCST. (j) Significant E/C decrement on the CPT (only computed for the 200 mg. dose). (k) Significant 400 mg./200 mg. and 200 mg./100 mg. decrement on the CPT.

Com The experiment was a 10 × 10 Latin Square. The objections described previously to the crossover design are not as important in this study where acute medications were used. The other drugs involved in this study were not included in this summary. Some of the data were evaluated by a one-tail test (b, c, and d, in RC). Only the 400 mg./200 mg. differences (c) are significant by a two-tail test. The use of per cent scores for tests (a) through (g) merits a more thorough description and discussion than was given in order to understand the effects of using the method.

Kornetsky, C., and Humphries, Ogretta: Psychological Effects of Centrally Acting Drugs in Man, J. Ment. Sc. 104:1093-1099, 1958.

Mirsky, A. F., Primac, D. W., and Bates, R.: The Effects of Chlorpromazine and Secobarbital on the C.P.T., J. Nerv. & Ment. Dis. 128:12-17, 1959.

HI (a) Specific measures, (b) subject × drug interaction.

Ss 12 normals; 5 males and 7 females. Age: M = 21.1, R = 18 to 30.

Med* Single (acute) administrations of 100 and 200 mg. (two replications) with a minimum of 1 day intervening between successive administrations.

Des Crossover design. Post-testing (between 1½ and 4 hours after medication).

Inst *Mirsky:* (a) Continuous performance test (CPT): four measures; (b) self-report and behavioral rating of sleepiness: very sleepy, moderately sleepy, not sleepy. *Kornetsky:* (c) modified digit symbol test from the Wechsler; (d) pursuit rotor; (e) hand steadiness; (f) tapping speed; (g) tachistoscoptic recognition of numbers; (h) number of hours asleep for from 4 to 21 hours after medication (a total observation period of 17 hours): recordings by nurses.

RC *Mirsky:* (a) Significant E/C impairment on CPT. (b) Significant E/C increase in sleepiness. (c) Significant 200 mg./100 mg. impairment on CPT. (d) Nonsignificant (p = 0.054) 200 mg./100 mg. increase in sleepiness. (e) No significant drug × subject interaction. *Kornetsky:* (f) Significant 200 mg. E/C impairment on digit symbol, hand steadiness, tapping speed, pursuit rotor, and tachistoscopic threshold. (g) Significant 100 mg. E/C impairment on hand steadiness, tapping speed, and pursuit rotor. (h) Significant E/C increase in sleep at both E levels. (i) Significant 200 mg./100 mg. impairment on hand steadiness, tapping speed, pursuit rotor, and tachistoscopic threshold. (j) "Substantial" correlations among drugs on tapping speed, hand steadiness, digit symbol, and pursuit rotor with original ability on the tasks partialled out.

Com The experiment was a treatment × subjects design, with two replications, in which the treatments (medications) were administered in a partially balanced order. The objections

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described previously to the crossover design are not as important in this study where acute medications were used. Evaluation of secobarbital was omitted from this summary.

Mirsky: The sleepiness ratings were evaluated by a one-tail test. There were no significant E/C or 200 mg./100 mg. differences by a two-tail test. It was not clear whether the CPT data were evaluated by a one- or a two-tail test. If a one-tail test was used, then the significant E/C impairment (a) holds for the 200 mg. level but not for the 100 mg. level by a two-tail test; the significant 200 mg./100 mg. decrement (c) is not significant by a two-tail test.

Kornetsky: The E/C comparisons (f, g, h) were evaluated by a one-tail test. There were no significant differences by a two-tail test. (Our conclusion is dictated by the experimenters' having presented the 0.10 level, by a two-tail test, as the only probability value.) It was not clear whether the 200 mg./100 mg. comparisons (i) were evaluated by a one- or a two-tail test. If a one-tail test was used, then there were no significant 200 mg./100 mg. differences.

The correlations among drugs (j) were not significant by a two-tail test. The median hours of sleep time for placebo, 100 and 200 mg. chlorpromazine, and 100 and 200 mg. secobarbital, respectively, were: 1.0, 4.5, 8.0, 0.5, 2.0. Considering that the recordings were made from 4 to 21 hours after medication, the data for placebo and secobarbital are unusual. It appears that additional directions or experimental conditions must have been utilized to account for the prolonged period of wakefulness. If so, they were not mentioned.

Kornetsky, C., Pettit, M., Wynne, R., and Evarts, E. V.: A Comparison of the Psychological Effects of Acute and Chronic Administration of Chlorpromazine and Secobarbital (Quinalbarbitone) in Schizophrenic Patients, J. Ment. Sc. 105:190-198, 1959.

HI Specific effects of acute medication.

Ss 12 male schizophrenics. Age: M = 30.1, R = 21 to 40. Hosp: M = 3.75, R = 1 to 11.5. Five subjects had been receiving chlorpromazine prior to the start of the experiment. Medications were withdrawn at least 2 weeks prior to the start of the experiment.

Med Single (acute) administrations of 100 and 200 mg. (two replications) with a minimum of 1 day intervening between successive administrations.

Des Crossover design. Post-testing (90 minutes after medication).

Inst (a) Modified digit symbol test from the Wechsler; (b) pursuit rotor; (c) tapping speed; (d) tachistoscopic recognition of numbers.

RC (a) Significant 200 mg. E/C impairment on pursuit rotor, tapping speed, and digit symbol. (b) Significant 200 mg./100 mg. impairment on pursuit rotor and digit symbol.

Com The experiment was a treatment × subjects design, with two replications, in which the treatments (medications) were administered in a partially balanced order. The objections described previously to the crossover design are not as important in this study where acute medications were used. The comparisons were presumably evaluated by a two-tail test, since no mention was made of the one-tail test. A second study utilizing chronic (2 weeks) medication with the same subjects was omitted from this summary. A crossover design was used and presented as a whole. Since the data for the first stage were not presented separately, this study does not provide usable data for our purposes.

Kovitz, B., Carter, J. T., and Addison, W. P.: A Comparison of Chlorpromazine and Reserpine in Chronic Psychosis, A.M.A. Arch. Neurol. & Psychiat. 74:467-471, 1955.

HI (a) General, (b) relative effectiveness with various syndromes.

Ss 100 subjects, mostly schizophrenics; 50 males and 50 females. Age: not mentioned. Hosp: M app. = 6.6.

Med Individual schedules for 6 weeks. Minimum = 100 mg., maximum = 650 mg.

Des Linear design. Weekly behavior ratings; Wechsler before and during (after 5 weeks of medication) or during and after (from 4 to 6 weeks after medication).

Inst (a) Clinical improvement: presumably based on weekly behavior ratings by attendants, nurses, and physicians; (b) Wechsler-Bellevue Intelligence Scale; (c) a record kept of the number of ECTs given.

RC Significant E/C improvement on all three measures.

Com This study was actually a crossover design utilizing 150 subjects in three groups: Group A received placebo for 12 weeks; group B received reserpine for 6 weeks, placebo for 4 weeks, and chlorpromazine for 6 weeks; group C received chlorpromazine for 6 weeks, placebo for 4 weeks, and reserpine for 6 weeks. The study was summarized here as if it consisted only of a placebo and a chlorpromazine group with a total duration of 6 weeks, with the exception of the RC section, which presents the experimenters' conclusions. A significant E/C clinical improvement was found when the data were recomputed for the first 6 weeks. The chi square evaluation of ECTs is not valid because of correlated frequencies. Further, it is not clear whether the chi square utilized the number of subjects receiving ECT or the number of ECTs received. We computed a Fisher exact chi square for the E and C subjects for the first 6 weeks on the assumption that the only subjects to receive ECT during the experiment were those who received ECT before the experiment. A nonsignificant E/C reduction in ECT was obtained for the 49 subjects ($p = 0.06$). No E/C conclusions can be made about the Wechsler scores: (a) The data were not presented for the first 6 weeks; (b) there was a discrepancy between the text and the data presented in the table; (c) the testing schedule used confounds the drug effect and the withdrawal effect. The interest in the relative effectiveness of chlorpromazine with various syndromes was not evaluated.

Levin, M. L.: A Comparison of the Effects of Phenobarbital, Promethazine, Chlorpromazine, and Placebo Upon Mental Hospital Patients, J. Consult. Psychol. 23:167-170, 1959.

HI (a) General, (b) withdrawal effect.

Ss 60 schizophrenics, males and females. Age: R = 21 to 50. Hosp: minimum of 2 years.

Med Constant schedule of 300 mg. for 4 months. Two-month follow-up during which all medication was omitted.

Des Linear design. Pre- and post-evaluations and 2-month follow-up evaluations.

Inst Wittenborn Psychiatric Rating Scale: nurses and aides.

RC No significant E/C differences.

Com This study actually used two additional groups (phenobarbital and promethazine). It is not clear to what degree this study meets the criterion of random assignment of subjects. "Because phenergan, placebo, and chlorpromazine became available on different dates, it was not possible to assign Ss in a purely random fashion." [p. 168.]

Little, J. C.: A Double-blind Controlled Comparison of the Effects of Chlorpromazine, Barbiturate and a Placebo in 142 Chronic Psychotic Inpatients, J. Ment. Sc. 104:334-349, 1958 [British]. A crossover design was used and analyzed as a whole. Since the data for the first stage were not presented separately, this study does not provide usable data for our purposes.

Mason-Browne, N. L.: Perphenazine—A Drug Modifying Consciousness, Am. J. Psychiat. 114:173-174, 1957 [Canadian].

Mason-Browne, N. L., and Borthwick, J. W.: Effect of Perphenazine (Trilafon) on Modification of Crude Consciousness, Dis. Nerv. System 18:300-306, 1957 [Canadian].

HI General.

Ss 48 subjects; 24 males and 24 females. No diagnostic categories were presented. The subjects were described as chronic patients, displaying anxiety, overactivity, or being nursing problems. Age: M = 41.4, R = 20 to 54. Hosp: M = 12.3, R = 1 to 36.

Med* Constant schedule of 75 mg. for 30 days.

Des Linear design. Pre- and post-testing and post-clinical evaluation.

Inst (a) Clinical evaluation (improved, unimproved, worse): based upon daily observation by the nursing staff and occupational therapist and pre- and post-clinical assessment by the psychiatrist; (b) anxiety cluster from the Wittenborn Psychiatric Rating Scale by the experimenter; (c) tapping and dotting; (d) digit symbol; (e) Porteus Maze; (f) digit span.

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RC No significant E/C improvement.
Com This study actually utilized a third group which received perphenazine. Although all three groups were used in the analyses, E/C evaluations can be easily made by the reader.

Mirsky, A. F., Primac, D. W., and Bates, R.: The Effects of Chlorpromazine and Secobarbital on the C.P.T., J. Nerv. & Ment. Dis. 128:12-17, 1959. See: Kornetsky and Humphries.

Primac, D. W., Mirsky, A. F., and Rosvold, H. E.: Effects of Centrally Acting Drugs on Two Tests of Brain Damage, A.M.A. Arch. Neurol. & Psychiat. 77:328-332, 1957. See: Kornetsky and coauthors.

Raymond, M. J., Lucas, C. J., Beesley, M. L., O'Connell, B. A., and Fraser Roberts, J. A.: A Trial of Five Tranquillizing Drugs in Psychoneurosis, Brit. M. J. 2:63-66, 1957 [British].
HI General.
Ss 51 outpatient neurotics. Sex breakdown and age not presented.
Med Constant schedule of 150 mg. for 2 weeks.
Des Crossover design. Daily evaluations.
Inst Self-ratings of drug effect: very poor, poor, none, good, very good.
RC No significant E/C difference.
Com This study actually used four additional medications (amylobarbitone, benactyzine, meprobamate, sedaltine) in a Latin Square design. It is included here because it provides a partial control for, and evaluation of, sequence effects. Each medication followed each other medication an equal number of times, resulting in the removal of 5 df from the within-subjects residual which could be attributed to sequence. It is still questionable that the average effect of a treatment in such a Latin Square design is equivalent to its direct effect as derived from a linear design. Lacking a uniformity trial, however, our best judgment is that this study provides usable data for our purposes. This study is outstanding in its sophistication and serious treatment of various aspects of the research problem. The Latin Square analysis utilized 42 subjects.

"Patients were allowed to reduce the dose but asked to continue taking some of the drug if possible. Some, however, did omit the drug altogether on some days. With the exception to be mentioned immediately, the minimum number of responses was seven. For these incomplete schedules the average response was accepted. The exception related to one drug, chlorpromazine. Six patients discontinued treatment after three to six days, but gave definite reasons for doing so; for example: 'Made me feel terrible; I did try,' and 'more tense and depressed.' As a definite explanation had been given, the forms were included, the score being, as before, the average of the responses before treatment was abandoned." [p. 5 of reprint.] The resulting reductions in medication were not described. From the quotation we conclude that there was a significant E/C deterioration.

Rinaldi, F., Rudy, L. H., and Himwich, H. E.: Clinical Evaluation of Azacyclonol, Chlorpromazine, and Reserpine on a Group of Chronic Psychotic Patients, Am. J. Psychiat. 112:678-683, 1956.

Rudy, L. H., Rinaldi, F., and Himwich, H. E.: Comparative Effects of Azacyclonol, Reserpine, and Chlorpromazine on Moderately Disturbed Psychotic Patients With Long Histories of Hospitalization, Psychiat. Res. Rep. 4:49-63, 1956.
A crossover design was used and analyzed as a whole. Since the data for the first stage were not presented separately, this study does not provide usable data for our purposes.

Rosner, H., Levine, S., Hess, H., and Kaye, H.: A Comparative Study of the Effect on Anxiety of Chlorpromazine, Reserpine, Phenobarbital, and a Placebo, J. Nerv. & Ment. Dis. 122:505-512, 1955.
HI Anxiety.

Ss 46 males (probably); about 75 per cent schizophrenics and 25 per cent neurotics. Age: M = 31.4, R app. = 18 to 60. Hosp: new admissions.
Med Constant schedule of 100 mg. for 30 days.
Des Linear design. Pre- and post-testing.
Inst (a) Anxiety self-rating scale; (b) psychiatric anxiety rating scale; (c) symptom checklist completed on the basis of a psychiatric interview; (d) critical flicker fusion; (e) weight.
RC No significant E/C differences.
Com This study actually used two additional medication groups.

Rudy, L. H., Rinaldi, F., and Himwich, H. E.: Comparative Effects of Azacyclonol, Reserpine, and Chlorpromazine on Moderately Disturbed Psychotic Patients With Long Histories of Hospitalization, Psychiat. Res. Rep. 4:49-63, 1956. See: Rinaldi, Rudy, and Himwich.

Salisbury, Barbara J., and Hare, E. H.: "Ritalin" and Chlorpromazine in Chronic Schizophrenia: A Controlled Clinical Trial, J. Ment. Sc. 103:830-834, 1957 [British].
A crossover design was used and analyzed as a whole. Since the data for the first stage were not presented separately, this study does not provide usable data for our purposes.

Shepherd, M., and Watt, D. C.: A Controlled Clinical Study of Chlorpromazine and Reserpine, J. Neurol. Neurosurg. & Psychiat. 19:232-235, 1956 [British].
HI General.
Ss 16 female schizophrenics. Age: M app. = 40.5, R app. = 27 to 52. Hosp: M app. = 15.8, R app. = 7 to 29.
Med Constant schedule of 300 mg. for 6 weeks.
Des Linear design. Post-ratings.
Inst Clinical rating (improved, unimproved, worse) based upon weekly clinical assessments, post-treatment interview, and conference with the nursing staff.
RC Significant E/C improvement.
Com This study was actually a crossover design utilizing 24 subjects in three groups: Group A received placebo (0.75 mg. of reserpine which the experimenters regarded as a placebo), reserpine, and chlorpromazine in sequence; group B received placebo, chlorpromazine, and reserpine in sequence; group C received chlorpromazine, placebo, and reserpine in sequence. All medication periods were 6 weeks in length. The study was summarized here as if it consisted only of a placebo and a chlorpromazine group with a total duration of 6 weeks, with the exception of the RC section, which presents the experimenters' conclusions. No significant E/C improvement was found when the data were recomputed for the first 6 weeks. The chi squares presented by the experimenters are not valid since they utilized correlated frequencies.

Smith, J. A., Christian, Dorothy, Rutherford, Avonell, and Mansfield, Elaine: A Comparison of Trifluprom azine (Vesprin), Chlorpromazine and Placebo in 85 Chronic Patients, Am. J. Psychiat. 115:253-254, 1958.
A crossover design was used and analyzed as a whole. Since the data for the first stage were not presented separately, this study does not provide usable data for our purposes.

Smith, J. A., Gouldman, C., Rutherford, Avonell, and Wolford, J.: Comparison of Two Phenothiazine Derivatives and a Barbiturate in Chronic Schizophrenia, A.M.A. Arch. Neurol. & Psychiat. 81:97-99, 1959.
A crossover design was used and analyzed as a whole. Since the data for the first stage were not presented separately, this study does not provide usable data for our purposes.

Thorpe, J. G., and Baker, A. A.: A Research Method to Assess a New Tranquilizing Drug, J. Ment. Sc. 102:790-795, 1956 [British].
HI General.

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Ss 24 female schizophrenics. Age: M = 42.6, all subjects less than 50. Hosp: M app. = 15, R app. = 3 to 29.

Med Standard schedule of 150 mg. for first 2 weeks and 300 mg. for the second 2 weeks. Total duration of 4 weeks.

Des Linear design. Testing before treatment and at the end of each 2-week period. E and C subjects were matched on each variable by analysis of covariance.

Inst (a) Behavior Rating Scale: by the junior author from nurses' observations, yielding two measures—schizophrenic deterioration and restlessness; (b) rating of tension: by the junior author from brief interview.

RC (a) Significant E/C reduction in restlessness at 2 and 4 weeks. (b) Significant E/C reduction in tension at 4 weeks. (c) No significant E/C differences among the three wards involved.

Com This study was primarily directed toward the evaluation of Pacatal. Four groups of 12 subjects each were utilized: those on Pacatal, on chlorpromazine, on no treatment, and on a Pacatal placebo. The experimenters found no significant differences in the drug effect among wards. Thereupon they evaluated the drug effect (methods) by using the methods × wards interaction as the error term. This provided a highly conservative test of significance, requiring that F = 5.41 with df = 3/5. If the residual had been utilized as an error term, as is appropriate in this case, the test of significance would have required that F = 2.88 with df = 3/35. Even when utilizing only two of the four groups, according to our interest, it would only require that F = 4.45 with df = 1/17. Their conservative evaluation may have been somewhat compensated by the fact that all the methods × wards interactions yielded F-ratios of less than one. It still seems likely, however, that the evaluation was conservative. The use of a Pacatal placebo against which to evaluate the chlorpromazine effect is less than optimal. A proper evaluation of such a procedure would require a thorough examination of the "double blind" method. At best, it would be a messy business.

Walsh, G. P., Walton, D., and Black, D. A.: The Relative Efficacy of "Vespral" and Chlorpromazine in the Treatment of a Group of Chronic Schizophrenic Patients, J. Ment. Sc. 105:199-209, 1959 [British].

HI (a) General, (b) activity-withdrawal.

Ss 44 female schizophrenics. Age: M = 39.7, R = 28 to 50. Hosp: M = 12.7, R = 1 to 25.

Med* Standard schedule for 8 weeks, increasing from 75 mg. the first week to 300 mg. the sixth, seventh, and eighth weeks.

Des Linear design. Weekly evaluations and post-treatment improvement rating. E and C subjects were matched on age, length of hospitalization, hospital adjustment, and the Rowell and Venables scales.

Inst (a) Rowell Psychiatric Behavior Scale by nurses; (b) Venables Activity-Withdrawal Scale by nurses; (c) improvement rating (four-point) by nurses.

RC No significant E/C differences.

Zeller, W. W., Graffagnino, P. N., Cullen, C. F., and Rietman, H. J.: Use of Chlorpromazine and Reserpine in the Treatment of Emotional Disorders, J.A.M.A. 160:179-184, 1956.

HI (a) Affect, (b) ideation, (c) behavior.

Ss 95 subjects. Sex distribution not mentioned. Mostly schizophrenics, some organics, neurotics, and depressives. Age and length of hospitalization not mentioned.

Med Individual schedules of 200 mg. or more for 1 month.

Des Linear design. Weekly ratings based upon complex and continuous observations and recordings. All subjects had received chlorpromazine for at least 1 month, and most for at least 7 months. About one-half of the subjects then received placebo for 1 month.

Inst Improvement rating (none, slight, moderate, marked) based upon cumulative data from: (a) Malamud-Sands: selected items completed by the physician on the basis of interviews two or three times a week; (b) weekly progress notes by the physician on ideation, affect, and behavior; (c) daily progress notes by nurses, educational and occupational therapists.

RC Significant E/C improvement.

Com This study was actually a withdrawal experiment investigating the effect of placebo after chlorpromazine medication. Thus, instead of the conclusion that there was a significant E/C improvement, the more appropriate conclusion is that there was a significant deterioration upon withdrawal of chlorpromazine. The interest in the effect of chlorpromazine on affect, ideation, and behavior was not evaluated in this study, at least not within the scope of this review. A separate sample was used without a placebo control. The description of the rating procedure was incomplete, i.e., no provision was mentioned for rating deterioration. Ratings of deterioration must have been made, since the resulting data were presented. This study is difficult to follow and more difficult to evaluate. The descriptions of subjects, amount and duration of medication, and instruments and evaluation procedure are not adequate.

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PUBLIC HEALTH ASPECTS OF CANCER CONTROL

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THE remarkable changes which have occurred in mortality and morbidity figures over the last 50 years in most countries are now well recognized. One of the most striking features is that diseases of the circulatory system, cancer, and violent deaths (i.e., accidents in traffic, homes, and industry) have replaced communicable diseases as the leading causes of death. This trend is most pronounced in countries with a relatively high standard of living and well-developed health services.

PROBLEMS IN CANCER CONTROL

It is, however, not only the increasing role played by cancer as a *cause of death* which has stimulated the interest of public health authorities toward the cancer problems. The encouraging strides forward in the understanding of the etiology of malignant tumors, opening the road to the *prevention* of certain types of cancer, and, even more significant, the results of surgical and radiologic *treatment* of the disease have placed before society a host of new tasks. The time has passed when public health services can leave the handling of malignant tumors to only the clinicians and pathologists. Control of cancer, in the widest sense of the term control, has in the last decades become an integral and important part of the health services of most countries. The epidemiologist and statistician, the occupational health specialist, and, last but not least, the public health administrator have entered the field.

Cancer is frequently listed with the "chronic" diseases. Such categorization gives little information as to the nature of any disease and the specific problems attached to it. Cancer, like any other chronic disease, presents the health administrator with a number of specific features which to a large extent cannot be handled jointly with the problems of other chronic diseases. The dramatic (at

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least psychologically) course of the disease, climaxing at the moment of detection, and the fact that optimal results of treatment depend more often than in most other chronic diseases on early correct diagnosis and immediate treatment by a team of highly skilled specialists, not seldom in need of costly equipment, provide a unique challenge to the health services. The widespread fear of cancer in the population and the willingness, therefore, of appropriating organizations to raise funds for the control of cancer have been utilized with great effect by foresighted public health administrators. By "selling" the idea of increased knowledge and better protection to the public, greatly improved cancer control systems have been developed in various parts of the world. In many countries also, large and active voluntary groups have devoted themselves to fighting the disease and donations have been forthcoming to an extent which is unparalleled for most other diseases. At the present time both the enlightened public and the responsible bodies of society request a plan and an organization for cancer control which were incomprehensible only a few decades ago.

To the public health administrator, improved control of cancer today presents a series of problems partly of simple, partly of more complex nature. These problems may be listed in many ways. Following is an attempt to very briefly enumerate them from the practical angle as they are met by those responsible for the proper functioning of the total health service of a country. Regardless of the system of health services, which varies from country to country with the administrative, social, and economic pattern of the country concerned, the public health administrator in an increasing number of countries will in the end be responsible for over-all planning and promotion of the various branches of the health services. Cancer control should be regarded as an integral part of such services.

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ETIOLOGY

A prerequisite for the prevention of cancer is wider and deeper knowledge of etiological factors in the production of malignant tumors. One of the most important functions of the public health service today, therefore, is to ascertain that epidemiologic, clinical, experimental, genetic, and other forms of *research* are carried out to clarify any etiological connection between certain environmental and other factors and cancer.

Great attention is being paid today to the possible causative relationship between the uses of tobacco and cancer, such as between lung cancer and smoking, between lip cancer and uses of certain types of pipes for smoking, between oral cancer and chewing of tobacco, etc. The role of air pollution in this connection is not yet known.

A vast field where definite results have already been obtained consists of occupational cancer hazards. There exists a long list of industries and other parts of the present-day productive machinery where certain causative factors of cancer have been defined and others are *sub judice*. As a matter of fact, it has been a shock to the public health administrator, to industrialists, and to workers to gradually realize how manifold is the threat of cancer in the various processes

of production on which our standard of living depends. Here a scientific basis for preventive measures has already been established (see PREVENTION).

Less yielding in scientific results on which practical public health steps may directly be based has, so far, been the research into the relationship between food habits and cancer. It is, however, generally accepted that such causative connections must be presumed to exist. Surveys present great difficulties, partly in view of the many factors involved in nutrition, partly in finding adequate control groups. Improved communications and world trade in prepared foods, with the concomitant rapid changes in indigenous food habits, also limit the possibilities of isolating and defining the role played by food habits in the causation of cancer. New problems arise as a result of industrially processed foods, food additives, synthetic food substitutes, etc.

Somewhat simpler is the study of the relationship between drinking habits, especially alcohol consumption, and the incidence of certain forms of malignant tumors in the digestive tract.

Some promise of success has been offered by surveys of the relation of breast cancer in women to number of children and nursing of babies. The study of variations in the incidence of cancer of the cervix uteri in relation to certain aspects of sexual habits and sexual hygiene in different ethnic groups also seems to open new vistas.

From the public health point of view, also, the study of any relationship between social status, general standard of living, and cancer is being followed with great interest.

A special group of problems has come to the foreground and has been accentuated in recent years, because of the increased radiation to which human beings are exposed as a result of fall-out from tests with nuclear weapons and the increased uses of radioactive material in industry, in medical therapy, and for scientific purposes generally. The need is felt more strongly than ever for establishing the "basic figures" for the occurrence of malignant tumors (produced perhaps partly by the naturally occurring background radiation), so that any increase in the incidence of certain types of cancer as a result of man-made sources of radiation may be identified. So far, attention first and foremost has been turned to leukemia, osteosarcoma, and cancer of the thyroid, but the problems in this field are both complex and intricate.

Other problems of etiology are the relationship between viruses and malignant tumors and between hormones and malignant tumors, the role of certain diseases as "trigger" factors for cancer, etc.

PREVENTION

As the causative agents of the various types of malignant tumors are gradually and slowly defined, prevention of cancer is gradually being put into practical operation. The greatest results have, so far, been achieved in the many industries where cancerogenic substances have been used either as raw materials, intermediary products, final products, or by-products or have simply been introduced during the productive process as tools. A very long list of dangerous substances have thus been eliminated in industry.

The classic case of chimney-sweeps' cancer was described by Percival Pott in 1775[1]; but it was 140 years before this was followed up by Yamagiwa and Itchikawa's experiments,[2] in which cancer was produced in rabbits by applying tar to the skin of the ears. Only after Cook and his colleagues[3] had demonstrated that tar products are strongly carcinogenic, however, was a long series of preventive steps in relation to tar and tar products introduced into industry.

At present more than 200 industrial carcinogens have been identified, but the list is increasing rapidly. Hueper[4] has undertaken an illustrative compilation of known cases of occupational cancer in Europe before and after 1928. Before 1928 he found 2,235 cases; after 1928, 7,231. From these figures it appears that the total number of known cases of occupational cancer is relatively small in relation to the total mortality of cancer in the countries concerned. It is generally recognized, however, that this partly reflects the difficulty of identifying the cause of a disease when it takes from years to decades for the disease to develop. It is a fact that the incidence of cancer is considerably higher in an industrial than in a rural population. In Denmark, the prevalence in industrial workers was found to be twice as high as in workers in agriculture, forestry, and fisheries.[5]

In consideration of the already known carcinogens, it is obvious that many industries are involved, including those producing metals and alloys, the chemical and electrochemical industry, canneries, breweries, the oil, fat, and tar industries, producers of wood pulp, cement, rubber, cosmetics, petroleum, and mineral oils, all industries using radioactive matter, and the tobacco industry. This list may easily be lengthened. As a matter of fact few industries will, on closer scrutiny, prove to be free of all carcinogens in their productive process.

In the "primary prevention" of cancer concentration must be on the elimination of, or protection against, known or suspected carcinogens in the environment of the population. The following list of groups of carcinogens is taken from Hueper[6]:

1. Chemical carcinogens
   - A. Organic chemicals

     Aromatic compounds: tar, pitch, asphalt, soot, shale oil, crude paraffin oil, anthracene oil, lubricating and fuel oils, greases, creosote, lamp black, aromatic amines (betanaphthylamine, benzidine, aniline?), benzol

     Aliphatic compounds
   - B. Inorganic chemicals

     Arsenicals, chromates, nickel carbonyl, asbestos
2. Physical carcinogens: ultraviolet rays, alpha and beta rays, gamma and x-rays
3. Nutritional disturbances involving protein, fat, and vitamin metabolism and affecting liver, pharynx, and thyroid

4. Biologic and undefined environmental carcinogens contained in betel quid, chaini, and *Schistosoma haematobium*

Changes in eating, smoking, and drinking habits also offer themselves as general approaches in prevention.

Whether further research in human genetics will open possibilities for eugenic measures for prevention of cancer is still an open problem.

Food additives, constituents of cosmetics, and sweetening substances (substitutes for sugar) also provide fertile ground for preventive measures.

Control of radiation hazards, starting with the old type of x-ray apparatus, has now widened to cover regulation of a host of radioactive sources and uses. The "health physicist" is a new type of specialist who is a regular member of the personnel in any large hospital, laboratory, reactor, or industrial plant which utilizes radioactive material in dangerous amounts.

It is of basic importance that the control of all sources of radiation rests with the public health authorities and not with those organizations which are instrumental in the further development of atomic energy for commercial and military purposes. Legislative action for such delineation of responsibility is under way in several countries where the public health authorities up until now have not had full control of this rapidly growing environmental hazard.

In spite of encouraging progress in these and other fields, however, we still have to admit that there is not at present too much that can be done to prevent the occurrence of cancer. Therefore, the attention of the health administrator is naturally turned toward the following measures.

EARLY DIAGNOSIS

It goes without saying that early detection and treatment of *precancerous lesions* represents an important step in protection against cancer. It has also been taken for granted that the provision of facilities for early and correct diagnosis of cancer (with subsequent treatment) is of vital importance for the *prevention of progress of the disease* and for good prognosis, not only *ad restitutionem*, but also *ad vitam* in the individual case. The matter is not so simple. For several types of malignant tumors, the question has not been answered with scientific evidence whether early diagnosis really improves the prognosis. Further intensive research in this respect—time- and money-consuming as it may be—may provide the health administrator of the future with a more secure platform for his practical approach.

Nevertheless, at the present time establishment of facilities for early diagnosis is one of the more obvious and important tasks of the public health administrator, and one for which the public as well as the clinicians are pressing.

Education of the public, not only in the basic facts of the causation and pathogenesis of cancer, but also in the interaction between the various parts of the cancer control system, is generally accepted as being essential to promote early diagnosis. The establishment of this fact is simple, but many are the complexities and sources of doubt when the health administrator tries to carry it out into practice. How is the public going to be educated? At what age? Who should undertake the education? What about repetition? How can one avoid

cancerophobia? To what extent does education of the public encourage quacks of various types to exploit commercially the fear of cancer?

Most countries today take the attitude that any cancerophobia that may be created has to be regarded as a transitional phenomenon, as a passing stage on the way to knowledge and a more rational attitude. Even within the medical profession itself, however, opinions have been divided on this point, and in some places the health administrator may for this reason find himself in an exposed position when he promulgates health education of the public.

Various methods of mass examination for early detection of cancer have been tried, but on the whole few generally accepted methods have, so far, been developed. Miniature x-ray of the stomach, for example, does not seem to offer results which justify the cost and the time spent. Mass miniature chest x-ray screening, which in some countries has been carried out on a very large scale to detect cases of tuberculosis of the lungs, will yield as a by-product a certain number of cases of tumors of the respiratory tract and has thus proved of value. However, to organize x-ray miniature screening of large groups of the population for the detection of cancer of the lung alone is out of the question.

A more promising approach seems to be mass examinations of smears from the cervix for cancer of the uterus and of smears from the respiratory tract and from the stomach for neoplasms of lung and stomach. So far, however, these methods, which also call for specialized personnel, have been used more for epidemiologic studies of certain types of cancer than for early diagnosis in larger groups of the population.

In many hospitals, of course, part of the routine examination upon admission aims at the early diagnosis of cancer, although there still is much room for improvement in this respect. Even such an obvious procedure as the exploration of the rectum with palpation of prostate in all male patients beyond a certain age is too often neglected. The same holds true for routine examination of female patients for cancer of the breast and genital organs.

"Multiphasic screening" of presumably healthy groups of the population has in recent years acquired great popularity in certain countries. Pregnant and nursing women, housewives generally, groups of industrial employees, sailors, fishermen, etc., elderly people, and parts of the general population have been exposed to such general, all-over medical examinations or "checkups." The results, as far as early detection of cancer is concerned, generally speaking do not seem to justify the time spent by medical personnel and the cost of these examinations. Such examinations, however, have generally been organized for a much broader purpose and may be useful in countries where the number of medical personnel and institutions is not so limited that their time is fully occupied by medical tasks of a higher priority.

The questions facing the public health administrator in this connection include whether facilities for early diagnosis should be established only in hospitals with outpatient departments, or whether they could also be profitably organized outside hospitals in various types of health centers. Also, it has to be decided who should be medically responsible under each system. Should such mass examinations be reserved for special groups, e.g., women over a certain

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age or men in certain occupations, or should they be open to everybody? The answer to this question will depend finally upon the epidemiologic situation as far as the various types of cancer are concerned.

Examination of the breast in women has been carried out in several countries on a mass scale, sometimes by cooperation between public health services and voluntary health organizations fighting cancer. This approach seems to have public appeal of great magnitude, and the attendance even under unfavorable conditions in rural areas has sometimes been strikingly high.

Such mass examinations are costly and time-consuming, and the question will always arise from the public health point of view as to whether medical personnel should be used for this purpose or whether other medical tasks deserve a higher priority. It is, therefore, strongly recommended that all such mass examination programs be carried out under full scientific planning and control so that conclusions may be drawn as to whether such methods for early diagnosis are recommendable. Such mass examinations, properly conducted and assessed, will also contribute toward answering the fundamental question of to what extent and for what types of cancer early diagnosis really improves the prognosis.

Another fundamental question is what role could be played by the "first line doctor," meaning the general practitioner in those countries where he is the medically trained person who gets in touch at first hand with a very large proportion of the population. That the general practitioner has a very important role to play is obvious, but the question arises in many countries as to whether his knowledge and diagnostic techniques are up to date and also whether some of the special methods, e.g., examination of smears, examination of the breast, collection of specimens for biopsy, etc., could accurately be performed by him.

The general belief in several countries for the time being seems to be that postgraduate training of general practitioners is necessary to brush up their knowledge and techniques for the early diagnosis of cancer. Methods requiring more intricate equipment and special training have generally been reserved for diagnostic centers for cancer. Such diagnostic centers for cancer have so far in most countries been located at existing hospitals. However, many hospitals need information on the best methods for early diagnosis of cancer, and health authorities often encourage teams of specialists from larger cancer centers to visit outlying or provincial hospitals to discuss with their colleagues how early diagnosis of cancer may be integrated with the work of the hospitals.

Postgraduate training of other groups of health personnel may also yield results. Important, for example, is the postgraduate training of dentists with the purpose of alerting them to precancerous lesions and early symptoms of oral cancer. Nurses, physiotherapists, etc., should also from time to time be given postgraduate training to sharpen their senses to and increase their knowledge of early symptoms of cancer.

Still lacking are reliable serologic or other biologic tests for early detection of cancer. Promising research is under way in this field, and the whole picture from the public health point of view may radically change as soon as reliable and inexpensive methods have been developed.

TREATMENT

Public health authorities responsible for the over-all organization of health services have in recent years been faced with several interesting problems in relation to treatment of cancer. Obviously a case of cancer may necessitate the joint action of a large team of highly specialized doctors and other groups of medical personnel to achieve optimal treatment of the disease. The encouraging development of therapeutic medicine in this field has been so rapid that the organization of medical institutions and personnel in many respects is lagging behind. Traditional lines for distribution of patients and excessive emphasis on professional prestige and vested interests may sometimes prevent an optimal solution.

Well known is the problem of establishing the proper cooperation between surgeon, radiologist, and pathologist; but the development of medicine in our days very often requires adding to the team more specialists: the neurosurgeon, the plastic surgeon, the abdominal surgeon, the anesthesiologist, the ear, nose, and throat specialist, and others as the situation may require.

The utilization of isotopes has created new problems in hospital design, in transportation, in handling of these powerful therapeutic agents, in personnel (the health physicist, technicians, etc.), and in the procedures of the hospital itself. These new problems are partially reflected in the fundamental question on which the health administrator must take a stand: Should treatment of cancer be *centralized* or *decentralized?*

Strong arguments are being brought forward in support of centralization: (1) The very complex and costly equipment needed in treatment of cancer, especially radiologic treatment, could not possibly be standard equipment in every hospital dealing with cancer. (2) In certain rare types of cancer, centralization is needed to develop at least in a few places sufficient knowledge and skill to provide optimal treatment. (3) The diagnosis and treatment of cancer generally require such high skills and specialization that the medical team necessary to cover all possibilities can only be established at sufficiently large treatment centers for cancer. (4) The desirability, at the present stage of development, of combining treatment with research calls for centralization of the treatment of cancer in specialized institutions.

Those in favor of decentralization of the treatment of cancer, on the other hand, will remind the health administrator of the fact that many cases of cancer may be treated with good results at ordinary hospitals and, further, that patients and their relatives in most cases prefer that the patient be treated near his home and by doctors whom he knows. Economic considerations will also favor decentralization.

In larger urban areas and also in other areas with a large population and good communications, the problem will be different than in countries with a more scattered population and smaller cities; but nowhere will the health administrator escape the question of to what extent centralization of cancer treatment should be encouraged.

An acceptable medical philosophy on this point seems to have been developed in certain countries where a distinction is made between diagnosis and treatment

in considering centralization. In Norway, the public health authorities have tried to apply the slogan: *Decentralization of diagnosis, centralization of selected cases of cancer*. This means, in practice, that every possible step should be taken to make all hospitals which might treat cancer adequate diagnostic centers for the disease. Once an exact and differentiated diagnosis has been established, the decision will have to be made as to whether the patient can safely be treated there or whether he should be transferred to a larger, more specialized treatment center. Not only the type of cancer but also its site, stage of development, and a series of other factors may enter into this decision. The responsible clinician is faced with one of the most difficult decisions any human being has to make: the delineation of one's own competence. The right decision, from the medical and ethical point of view, will often be made even more difficult by the trust the patient and his relatives have in the local hospital and by the desire of the patient to be treated near his home. On the other hand, with the growing public knowledge of cancer, the more highly educated patient will frequently exert a certain amount of pressure in the other direction, namely, to be sent to a larger treatment center.

The trend in many countries is now obviously toward centralization of at least the more complicated and rare cases of cancer.

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AFTERTREATMENT

Adequate treatment of cancer, more than treatment of many other diseases, necessitates well-organized, systematic aftertreatment. The public health administrator will have to consider three main types of medical activity in this respect: (1) control of further development of the disease, (2) aftertreatment, especially radiologic, and (3) rehabilitation of the patient.

The full utilization of scientific knowledge and applied medical practice in these three important fields is often neglected, and it may generally be said that the treatment of cancer in the acute stage is further developed on the whole than the various phases of aftertreatment. Again the difficult question of centralization or decentralization arises, because control, aftertreatment, and rehabilitation in many cases will call for equipment and personnel which are not to be found at smaller, local medical units. On the other hand, distance will often prevent the patient from traveling back and forth from his home to the place where proper aftertreatment can be administered.

Optimal radiologic aftertreatment will often be possible only at larger radiologic centers, although with the further development of therapeutic equipment, a higher degree of decentralization will be possible.

Rehabilitation, in many cases, represents the weakest link in the present medical organization, and the health administrator should have his attention keenly directed to this point. Too many patients with cancer now undergo excellent treatment in a well-equipped clinical center or hospital, only to be left thereafter to themselves weakened and sometimes partly disabled. Not only is valuable time lost but, from the psychologic and social point of view, the best period for motivating the patient for rehabilitation is also lost. When after some

time the patient, his relatives, and his local doctor realize that rehabilitation is necessary, the task is much more complicated and sometimes insoluble.

It is, therefore, of vital importance that any treatment center, large or small, should be rehabilitation-minded *from the very first day of treatment*, even if full rehabilitation with all its medical, educational, psychologic, and technical aspects in more complicated cases can only be undertaken at a specialized rehabilitation center. Both patient and doctor will thereby be keenly aware of the importance of rehabilitation as an integral part of the adequate treatment of many cases of cancer.

AFTERCARE

Quite a number of patients suffering from cancer cannot be fully cured or, even if they are cured of their disease, cannot be fully rehabilitated. They will need care, either in their own home, in nursing homes, or elsewhere. To secure proper aftercare, special types of auxilliary personnel including social workers, home visitors, etc., have been developed.

As a general rule aftercare institutions for cancer patients should not be established as a nosological entity. Patients suffering from cancer and in need of care should be cared for along with chronically ill and aged patients with other diseases.

Experience in several countries has shown that cancer patients in need of care profit greatly if social workers, home visitors, etc., have been trained specifically in the problems of cancer patients.

COMBINED CENTERS FOR DIAGNOSIS, TREATMENT, AND RESEARCH

The fundamental need for further research in cancer etiology, treatment, and aftertreatment is recognized by health authorities in most countries. There also seems to be general agreement that one way of promoting research is to establish combined centers for diagnosis, treatment, and research at one institution. Such a combined cancer center will, therefore, include at least the following main groups of activity: (1) diagnostic services for inpatients and outpatients, including special facilities for early diagnosis; (2) treatment facilities for inpatients and outpatients, which should be highly specialized, in the form of teams; (3) research units covering basic sciences (biochemistry, biophysics, radiobiology) as well as applied clinical sciences, pathology, and histology; (4) experimental units where surgeons, radiologists, pathologists, toxicologists, endocrinologists, etc., may undertake experimental research; (5) departments for cancer registry and special field research projects; and (6) a unit for information and education of the public.

The establishment of a full combined cancer center of this type requires considerable capital investment, and only few countries, so far, have succeeded in establishing a sufficient number of them. Where they have been established, however, the results are very encouraging indeed.

UTILIZATION OF VOLUNTARY AGENCIES

The public health administrator will also have to consider to what extent and for what purposes voluntary agencies can be utilized in the combat of cancer. Excellent results have been achieved in several countries by voluntary agencies, especially in the fields of education of the public, introduction of mass examination schemes, raising of funds for research and treatment, and assisting and creating interest in epidemiologic research. Also, voluntary agencies in various countries gradually are now turning more of their attention toward rehabilitation and aftercare of cancer patients.

STATISTICS OF CANCER

The public health authorities responsible for planning and establishing the various types of cancer services which have been briefly discussed will not be in a position to fulfill that task unless adequate statistical data on the prevalence and incidence of cancer are forthcoming. An adequate description of the incidence of cancer in a population requires not only enumeration of the cancer cases or cancer deaths, but also enumeration of the population in which the cases or deaths occur. Health statistics and demographic statistics must go hand in hand, and only when both are adequately developed is it possible to supply the health authorities with the statistical material required for rational planning.

The account which follows deals with the situation in European countries, where vital statistics systems have been established.

Until recently, knowledge of the occurrence of cancer in various regions and knowledge of the public health importance of cancer had to be based mainly on statistical studies of *mortality data*. Since the 1930s and especially in the last 10 years, these investigations to an increasing extent have been supplemented by statistical analyses of *morbidity data* from varying sources.

CANCER MORTALITY STATISTICS

The official death certificates, collected and analyzed by some central institution in each country, provide the source material for national mortality statistics. The majority of European countries have produced cancer mortality statistics for many years, some countries since long before the turn of the century. In spite of their obvious shortcomings, mortality statistics represent the best material available for retrospective studies of the impact of cancer throughout the years. In many countries such studies of mortality trends are difficult to carry out because of the territorial changes that have taken place. Assessment of the mortality trends for the various forms of cancer is complicated to some extent by changes, from time to time, in the definition of cancer and the classification of tumors. The steady improvement in diagnosis of cancer and the advances in therapy have naturally had an influence on the recorded cancer mortality, the extent differing for the various forms of cancer.

Table I surveys trends in total cancer mortality in several European countries.[7,8] Rates are not age-adjusted. The effect of age-adjustment would differ in the various countries. For example, total cancer mortality per 100,000 in Norway

TABLE I. MORTALITY FROM CANCER AND ALLIED CONDITIONS IN SOME EUROPEAN COUNTRIES, BOTH SEXES

A. CRUDE DEATH RATES PER 100,000 POPULATION PER YEAR

YEAR	GERMANY	ENGLAND AND WALES	BELGIUM	DENMARK	SCOTLAND	SPAIN	FINLAND	FRANCE	IRELAND	ITALY	NORWAY	NETHERLANDS	PORTUGAL	SWEDEN	SWITZERLAND
1905	72.9	88.9	59.4	——	90.0	45.4	——	69.5‡	——	58.3	97.4	101.2	22.3	——	129.6
1915	77.2	112.1	——	——	110.9	56.7	——	70.8	——	66.6	96.7	109.0	25.8	110.0	125.9
1925	101.9	133.4	83.5	137.5	137.1	64.5	——	74.2	93.8	58.1	118.6	113.3	34.1	120.0	144.6
1935	145.2	154.0	109.3	146.2	157.4	68.5	86.8	94.8	118.6	82.0	126.7	126.2	49.0	131.6	161.7
1945	141.4*†	193.3	125.2	161.5	175.4	66.8	118.4	153.2	133.9	90.1	131.2	132.5	45.4	141.1	181.3
1955	189.4†	205.5	207.5	190.6	206.2	——	145.8	183.8	161.4	128.2	158.9	154.8	84.1	164.1	189.6

B. PERCENTAGE OF ALL DEATHS STATISTICALLY ATTRIBUTED TO CANCER AND ALLIED CONDITIONS

YEAR	GERMANY	ENGLAND AND WALES	BELGIUM	DENMARK	SCOTLAND	SPAIN	FINLAND	FRANCE	IRELAND	ITALY	NORWAY	NETHERLANDS	PORTUGAL	SWEDEN	SWITZERLAND
1901	3.7§	4.4	3.4¶	——	4.6	1.5	——	3.5‡	3.4	2.4	6.4	5.4	1.2**	7.6††	7.1
1920	5.8	9.4	5.4	10.5	8.5	2.5	4.5#	4.7	5.7	3.7	8.6	9.4	1.2	8.6	9.3
1947	15.0‖†	15.1	10.1	16.2	13.7	5.9	10.1	11.9	9.0	8.5	15.3	16.4	3.6	13.0	15.7
1955	18.2	18.2	16.7	21.2	17.2	——	16.0	15.3	13.3	14.1	18.9	20.6	7.7	17.1	19.0

***1946**
†Federal Republic of Germany
‡1906
§1905
‖1948
¶1903
#1927
****1902**
††1913

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showed an increase from 105 in 1920 to 159 in 1955, i.e., an increase of 50 per cent. On age-adjustment this increase is reduced to approximately 15 per cent. From a public health point of view, however, the crude mortality rate for cancer is an important index, since it correctly shows the recorded cancer mortality under the conditions which actually existed during the particular periods under consideration.

From available statistics, it appears that the recorded cancer mortality in 1955 varied greatly from country to country in Europe, from 84.1 per 100,000 in Portugal to 233.9 per 100,000 in Austria. Some of the variation can be explained by differences in the age distribution of the populations. Variations in diagnostic standards in different countries no doubt also play a part. It seems certain, however, that real regional variations exist, although very little research has been carried out in this field.

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In spite of these considerable variations in the total recorded cancer mortality in the various European countries, in all these countries cancer is now one of the main causes of death, second only to deaths due to diseases of the circulatory system. In the majority of countries cancer accounts for 15 to 20 per cent of all deaths.

Cancer is generally regarded as a disease of older age groups. Mortality statistics show, however, that this disease plays an important role as cause of death both in childhood and in middle age. In many European countries more than 30 per cent of all deaths from disease in the age group 40 to 59 years are ascribed to cancer. From 60 years of age upward, the proportional mortality from cancer decreases rapidly, but nevertheless the *risk* of dying from cancer rises throughout life. The decline in proportional mortality after 60 years of age is due to the rapidly increasing risk in old age of dying from diseases other than cancer, primarily diseases of the circulatory system.

Mortality statistics have been used quite extensively as a basis for studies of group variations in cancer mortality within countries. The comprehensive analyses of regional and social class variations in cancer mortality carried out by the Registrar-General of England and Wales in conjunction with the census is an excellent example and may serve as a prototype.

These and similar investigations resulted in the discovery of important trends in cancer epidemiology. In the 1930s, for example, an increase in recorded mortality from lung cancer was noted, and the characteristic pattern of the mortality by age, sex, and urban/rural residence was described. Ten years later these epidemiologic trends were reluctantly accepted as real and have since played an important part in discussions on the causes of the increase in lung cancer mortality. The question of whether or when death certificates can be relied upon for epidemiologic studies has often been raised, but the fact is that observations made by the Registrar-General in his Decennial Supplements for 1920 and 1930 have been largely confirmed by later studies with supposedly more reliable morbidity materials.

One may also mention the use of death certificates and mortality statistics for more special purposes, i.e., investigating occupational cancer risks. In some typical studies of this kind, death certificates have been used for information

on the number of deaths observed from a specific form of cancer within the population at risk, while the official mortality statistics have been used to calculate the expected number of deaths in the same population within a specified time. As illustrations, one may quote the demonstration of an occupational risk of cancer of the urinary bladder in certain categories of workers in the rubber industry[9] and of a high risk of lung cancer among some asbestos workers.[10]

As a conclusion to these remarks, which are in no way complete, it can be stated that mortality statistics have been, and still are, of the greatest significance in the description of and research into cancer as a health problem. Steady improvements in the statistical classification of tumors and increasing differentiation of statistics are opening up new possibilities for the use of mortality statistics. For many purposes, however, mortality statistics are inadequate, partly because they fail to cover important aspects of the cancer problem and partly because it is so often difficult to know the conditions under which and the degree to which the data can be trusted. The most important deficiencies and weaknesses inherent in the official cancer mortality statistics may be summarized as follows:

1. The various forms of cancer exhibit extreme differences in fatality rates. While some forms of cancer invariably seem to be fatal, in other forms the percentage of patients who are apparently cured may be well over 50 per cent—in the case of skin cancer, even over 95 per cent. The majority of cancer patients belong to age groups where the risk of dying from causes other than cancer is very high. Accordingly, many of them succumb to other diseases while the cancer is temporarily arrested or actually progressing, and under these circumstances cancer may not be mentioned on the death certificate. It is obvious, therefore, that cancer mortality statistics will always give an incomplete and somewhat distorted picture of the occurrence of cancer, and it is conceivable that for some forms of cancer mortality materials may be biased to such an extent that they are actually invalid for some purposes. So far there have been no systematic studies of these problems.

2. Death certificates contain no information as to which examinations and findings the diagnoses were based on. Statistical classification of such material is likely to result in very heterogeneous groups. Important epidemiologic features may be masked or, conversely, one may be misled by false associations. The traditional criticism of cancer mortality statistics has often focused on this point. Not to be neglected in this connection is the resulting *uncertainty* which characteristically may express itself in a very reluctant reaction—or complete lack of reaction—to the important epidemiologic leads which cancer mortality statistics sometimes offer.

3. Death certificates contain no information on the stage in which the diagnosis was established or about the treatment which may have been given.

4. Not only medical information but also personal characteristics are very scanty on the death certificates, and they are difficult to supplement after death.

5. Considering the characteristics of cancer and the problems related to its etiology, pathogenesis, and treatment, it is of utmost importance that interest should be directed toward the very earliest phases of the morbid process. It is clearly unsatisfactory that the best material available for statistical studies

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of the occurrence of this disease is based on its end results. The limitations of the official mortality statistics which have been pointed out above emphasize the need for statistical material that can give a more detailed, complete, and correct picture of the cancer problem. This can only be obtained by means of carefully designed studies of *cancer morbidity* in the population.

CANCER MORBIDITY STATISTICS

From the preceding discussion it follows that what is really needed is morbidity material, which should include all cases of cancer diagnosed for the first time during a given period of time in the defined population or all diagnosed cases of cancer in existence at any time during the period. The statistical analysis could then be based on all known cases of cancer, and it would also be possible to undertake more detailed studies of exactly defined samples of the cases.

The requirements which have been stated above apply regardless of whether one is primarily interested in studying diagnosis, treatment, and results of treatment of cancer in the population or in obtaining good estimates of the incidence and prevalence of cancer. Provided the collection of data can be organized effectively, the reliability of the estimates will depend only on the quality and distribution of diagnostic services.

The collection of cancer morbidity material as defined is always a very difficult and comprehensive undertaking which makes great demands on personnel and requires a good deal of organization, cooperation, and funds. It may be pertinent to point out, therefore, that only on the basis of such a material will it be possible at last to study systematically the validity, for various statistical and epidemiologic purposes, of other materials that are more readily available, such as the official death certificates, hospital materials, biopsy materials, or postmortem series.

Information about the cancer cases in the population can be obtained by cancer registration or by means of special surveys. Both of these procedures may be supplemented by screening examinations. While the two first-mentioned procedures consist of collecting information on cases already diagnosed, screening aims at detecting as many as possible of the previously unknown cases among the population. Only cancer registration will be fully discussed here.

Cancer Registration.—The terms cancer registry and cancer registration at present cover several institutions and projects which differ greatly in aims, design, and comprehensiveness. At one end of the scale is the purely local register found in an increasing number of special hospitals, and at the other end, the complicated national central register for material from all available sources within its area. Local registers are in the nature of hospital files which help to maintain close contact between the hospital and its cancer patients, with a view to patient supervision and to a build-up of detailed data on the efficacy of different treatment methods. On the other hand, national registries as found in Scandinavia, for example, serve a purely statistical purpose and are primarily concerned with the study of cancer as a mass phenomenon, not with individual patients. Only this kind of cancer registry will be discussed here. Such central

registries, more or less effective and with varying programs, are to be found in Australia, Canada, Israel, New Zealand, the Union of South Africa, a number of states of the United States, and in Europe, in Austria, Belgium, Denmark, England and Wales, Federal Republic of Germany, Finland, France, Iceland, the Netherlands, Norway, Scotland, Sweden, and Yugoslavia. Most of these registries have been started within the last 10 years. In some places cancer registration covers the entire population; elsewhere it is limited to certain areas or based on selected hospitals. As a rule the registries are set up by health authorities, but the Belgian, Danish, Finnish, and Icelandic registries are run by voluntary cancer organizations, while in Norway the registry is run jointly by public and private institutions under the direction of the Director-General of the Public Health Service. In the Netherlands, the Municipal University of Amsterdam operates a cancer registry with cooperating hospitals. In the United States and Canada, cancer registration is based partly on compulsory and partly on voluntary notification of cases. Of the European countries listed above, only Norway has introduced compulsory cancer registration.

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The financial arrangements for registration vary widely in the various countries. In the United States the individual state governments cover the expenses, usually with support from the U. S. Public Health Service (National Cancer Institute) and the American Cancer Society. Some states pay for notifications. Either a definite sum may be paid for each case reported, as in California, a point system may be used, as in Connecticut, or special grants may be made to the institutions participating in the registration. In all cases the aim is to contribute toward the cost of office work required to maintain registries at the various hospitals. In Belgium, Denmark, Finland, Iceland, and Norway the national cancer associations take care of most of the registration expenses, while the national government usually makes contributions, partly in the form of direct appropriations, partly by mechanically processing the material free of charge. In the other European countries the national government appears to cover all costs. The only European countries where a fee is paid for individual reports are Denmark, Finland, and Iceland. In Norway, payment is made under certain circumstances. In the United Kingdom, peripheral registration is based on the regional cancer centers and the National Health Service supplies personnel for office work, records, and follow-up.

Aims: The aims of cancer registration are clearly stated in the Report on the Second Session of the WHO Expert Committee on Health Statistics.[11] The Committee emphasized the value of systems of registration and follow-up of cancer patients at hospitals and similar institutions in Canada, Denmark, France, Norway, the United Kingdom, and certain areas of the United States. Such projects were believed to be of great value "(a) for improving the possibility that patients developing cancer shall in the future receive the earliest and best treatment available, (b) for increasing knowledge of cancer morbidity and its relationship with social and environmental factors, (c) for providing indications for scientific studies on particular points of the etiology of cancer, and (d) for ascertaining the prospects of survival and apparent recovery with a view to measuring in the future the value of steps taken to secure earlier and better treatment."

Emphasis on the work to be undertaken by a cancer registry varies from country to country. For example, the United Kingdom registry has so far concentrated on studies of treatment and survival, and one of the main reasons for starting registration was to establish a follow-up system at hospitals treating cancer patients. The Danish Registry, on the other hand, has concentrated almost exclusively on studies of cancer incidence and epidemiology. We shall comment briefly on both of these important functions of cancer registries.

Epidemiologic studies have from time to time during the past 200 years led to notable strides in cancer control. Observations made in such studies have often provided the basis for new and fruitful hypotheses concerning the etiology of cancer and have thus acted as a stimulus to experimental cancer research. There are several well-known examples showing that epidemiologic observations have directly led to effective prevention of certain forms of cancer. In recent years, application of the epidemiologic method in a number of excellent studies of the role of environmental factors in the causation of lung cancer has yielded a most convincing demonstration of the results that can be achieved by this method. Experience as well as theoretic considerations certainly indicate that a more systematic exploration of the epidemiologic method in cancer research might be highly rewarding, and a number of the existing cancer registries, including that of Norway, consider this their most promising and interesting task.

It is sometimes maintained that *studies of survival* based on data from a national or regional cancer registry must be superficial and inaccurate, since, of necessity, some of the details which should be taken into consideration in an exhaustive analysis will be lacking. Admittedly, statistical studies carried out in a specialized hospital department may bring out details that can hardly be obtained from data collected by routine reporting from many hospitals over a large area. Specialized hospitals treating cancer patients should therefore, by all means, be encouraged to do their own survival studies. Interest in follow-up and statistical analyses, however, tends to be somewhat sporadic in many hospitals, and one should also bear in mind that only very few hospitals can collect, over a reasonable number of years, enough cases of a specific form of cancer to be able to undertake a differentiated analysis. Furthermore, in view of the selection which is invariably present in hospital materials, it is always difficult to know when it is permissible to generalize from studies of such materials.

It is doubtless of some interest to know what results can be obtained by individual, highly skilled specialists dealing with selected materials, but it is at least as important to know, for example, what proportion of all cancer patients are receiving any specific treatment at all and the survival experience of the great majority of patients who are treated by the average surgeon or radiologist. The latter type of information can only be obtained by some kind of cancer registration. Satisfactory cancer registration makes it possible, in addition, to examine the extent and significance of selection in the materials of individual hospitals serving the population under study. A special function of the cancer registry regarding survival statistics, therefore, is to provide the general background, or the base line, for the more detailed statistics produced now and again by some of the larger specialized hospitals. To avoid any misunderstanding,

it should be pointed out that even the most perfect cancer registration cannot replace or render superfluous the accurate testing of different methods of treatment by carefully designed clinical trials.

In the course of a few years, cancer registries have been able to increase considerably our knowledge of the cancer incidence in various population groups. The information obtained by the registries on the individual patient, however, is very limited, and routine analysis meanwhile has usually had to follow the broad classifications usual in administrative statistics, i.e., an analysis of cancer risk in terms of sex, age, civil status, residence, and last occupation. This difficulty can be overcome in various ways: for example, by collecting additional information on all patients, or possibly a representative sample of patients, suffering from the special form of cancer under study and information on suitable control groups drawn from the population. This method naturally supplements routine cancer registration and has been successfully used in a number of special studies in various countries.

Methods: Detailed descriptions of the methods employed by various cancer registries can be found in WHO publications[12,13]; therefore, the main points of methodology will just be outlined here.

Registry material is obtained from the following sources: (1) hospital units, including outpatient departments, which diagnose and treat cancer, (2) pathologic laboratories (biopsies and postmortem examinations), (3) general practitioners, and (4) official death certificates.

Some registries (e.g., New York State, Norway) use all these sources of information; others (e.g., Connecticut, Denmark) feel that satisfactory registration is possible without bothering the general practitioner. Still other registries (e.g., California, England) are based only on a selection of the hospitals treating cancer patients.

Of course, if several independent sources of information are used, there will be overlapping; consequently the registry must have a highly trained staff and a very efficient filing system to avoid duplication. Independent reporting from various sources increases the likelihood that all known cases will eventually be registered and also tends to provide more accurate information about individual cases. For example, histologic diagnoses and pathologic findings are likely to be reported more accurately and in greater detail by a pathologist than by a clinical unit.

The information contained in the initial report from clinical departments is fairly uniform in the various countries, and usually includes the following: (1) name of hospital, (2) full name of patient, (3) sex, (4) date of birth, (5) birthplace, (6) residence, (7) civil status, (8) present or last occupation, (9) description of initial symptoms, (10) date of first symptoms, (11) date of first consulting a doctor, (12) time of establishing diagnosis, (13) time of commencing treatment, (14) site of primary tumor, (15) clinical stage, (16) histologic diagnosis, (17) examinations on which diagnosis is based, (18) information on treatment, and (19) for female patients, details of parity and age at menarche and menopause.

Registries in the United States usually request information on nationality of parents and race and religion of patients.

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Registries mainly interested in survival statistics usually have special short forms for an annual follow-up of cases already registered. In Norway renotification is required each time the patient is admitted to hospital. This is a considerable burden on the reporters and registry, but it increases the chances that all known cases will eventually be included. Renotification also helps to keep the registry informed of any changes in diagnosis, supplementary treatment, and the fate of the patient.

Only a few registries obtain direct information from the pathology laboratories on biopsy and autopsy findings. In countries where pathologists are interested in cancer registration, as in Norway, these reports are found to be very valuable both for increasing the completeness of registration and improving the quality of the material. In some places in the United States, biopsy material is sent in with the report (Texas and the noteworthy Tumor Registry of the Armed Forces Institute of Pathology).

In New York State practicing doctors are obligated to report cases of cancer among their patients. Elsewhere, doctors outside hospital are not much involved in cancer registration in spite of the fact that in every country a considerable proportion of known cancer patients are never hospitalized. It is usually assumed that the great majority of cancer patients who have not been treated in hospital will die of, or with, the cancer, so that a satisfactory registration of such cases where diagnosed will be obtained by a systematic study of death certificates. Obviously many cases, especially of skin cancer, may therefore go unregistered.

Most cancer registries use the official death certificates, for detecting cases not previously registered and for information on the time and recorded cause of death of previously registered cases. If cancer is mentioned on the death certificate of an unreported case, the certificate is most usually taken as a basis for registration. In Norway the doctor who signed the death certificate is always contacted, since it is considered important to have as much information as possible on these patients, most of whom were never hospitalized.

Filing systems and technical equipment vary greatly from registry to registry and will not be discussed here. Access to statistical machines for sorting and tabulation is necessary in order to make full use of the material. In the United States, all registries are completely equipped with statistical machines, so that special analyses can be undertaken whenever the need arises. European registries usually depend on the statistical machinery of other bodies, for example, a central statistical institution.

Effectiveness of cancer registration: Whatever the methods used, cancer registry material cannot give a complete picture of the incidence of cancer in a population. Some cases, including all those undiagnosed, will always escape registration. The number of undiagnosed cases cannot be known, and an estimate could be made only on the basis of special surveys including autopsies of a representative sample of all persons dying in the population concerned. It is important to bear in mind that the percentage of undiagnosed cases probably varies from country to country and within each country.

Errors may also occur in the registration of known cases. A varying number of cases will escape registration for different reasons and in different ways. Among

registered cases, information on the site of the primary tumor will sometimes be incorrect and noncancer cases may be inadvertently registered as cases of cancer. The frequency of errors is not known. It is again important to remember that the relative frequency of errors is likely to show regional and social class variations.

There is a real need for systematic investigation into the completeness and reliability of registry material. Lacking such investigations, which would be difficult to carry out, assessments must be based partly on very uncertain indices such as the ratio between registered morbidity and recorded mortality and partly on a more general consideration of the community where the registration is undertaken and of the methods used for it.

It is perhaps appropriate to conclude this survey by referring to the recommendations in the Fifth Report of the WHO Expert Committee on Health Statistics[14]:

> "The Expert Committee on Health Statistics,
>
> Having reviewed the existing situation in the countries which have for some years maintained cancer registers and recognizing that under the variety of conditions prevailing in different areas of the world a standard system cannot be suggested at this time,
>
> RECOMMENDS
>
> (1) that the different systems and methods of cancer registration be kept constantly under review by WHO so as to ascertain the best organizational structure to meet the basic purposes of cancer registers, and
> (2) that the information at present available be widely distributed by WHO among national committees on vital and health statistics and similar bodies."

Morbidity Surveys.—As mentioned, information on the incidence and prevalence of cancer can also be obtained by morbidity surveys. In one study of this kind, people are interviewed to ascertain the number of cases arising or existing during a given period. Interviewing is usually limited to a sample of households and an inference is drawn of the incidence and prevalence of disease in the total population. Sample surveys like this, of which the Danish Health Survey is a typical example, are usually designed to provide information on all diseases, not just cancer. They may provide valuable all-round health information, but they cannot be expected to yield accurate and detailed data on any specific disease unless, as was done in Denmark, doctors and hospitals are asked for further information on a sample of the cases found by interviewing.

A more appropriate method for determining cancer morbidity is to make a thorough canvass of doctors and hospitals in a given area for information on all cases of cancer detected, treated, or checked by them in a given time, for example, a year. This method was successfully used in the "Ten Cities Survey" in the United States in 1937 and 1947,[15] later also in Iowa and under entirely different conditions in Uganda in Africa. Such surveys can yield material comparable in

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type and quality to that of a permanent cancer registry, but they are typical sporadic investigations requiring very active data collection by a relatively large and skilled staff. The temporary character of the survey has advantages and disadvantages. Doctors may be more willing to cooperate in an intense short-term investigation than in registration extending over years. Its main disadvantage, compared with cancer registration, is that a single survey is useless for a study of the trends of cancer incidence in time; but to remedy this the survey can be repeated every decade, as was done in the "Ten Cities Survey."

Mass Screening Examinations.—Screening aims at revealing unknown cases of disease in the population, particularly early preclinical cases likely to respond favorably to treatment. Screening must be considered not as an alternative but as a possible supplement to the methods previously described of measuring cancer incidence. In particular, an effective screening program may disclose existing regional or other differences in the effectiveness of ordinary cancer case-finding, with the result that a check can be made on the validity of some of the variations in cancer incidence shown by cancer registry material, such as urban-rural, sex, and social class variations. A check of this kind is urgently needed.

The main requirement for effective screening is screening tests which are sufficiently sensitive and specific, yet suitable for application in mass surveys. They should preferably be applicable by technicians and other nonprofessional personnel. At the present time, as is well known, vaginal cytology for the detection of uterine cancer is the one apparently suitable technique for general application. The development of new screening tests is highly desirable therapeutically, statistically, and epidemiologically.

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Infectious Diseases

THE RELATIONSHIP OF TETANUS TO CHRONIC SKIN ULCERS AND DIABETES MELLITUS

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FLORIDA has the dubious distinction of having the highest tetanus morbidity rate in the United States.[1] The reasons for this remain to be discovered. Recent Florida studies indicate that a particular liability to tetanus infection exists in persons with chronic ulcerative lesions of the skin and/or diabetes mellitus. Both of these diseases occur most commonly in individuals over age 40, and the case fatality rates for tetanus patients in this age category are high. Adequate methods exist which will either prevent tetanus or mitigate its severity. Consequently, it seems desirable to direct the attention of practitioners everywhere to the peculiar liability to tetanus of patients with these conditions and to the need of utilizing preventive techniques.

EPIDEMIOLOGIC STUDIES

From 1943 to 1957, there were 170 cases of tetanus reported in Dade County, Florida, of which 93 terminated fatally. The reported cases were thoroughly investigated, using hospital charts, autopsy reports, death certificates, and epidemiologic reports as sources of information. Clinical histories were not available in 16 recorded cases because some patients arrived moribund, hospitals had closed, or charts could not be located.

Tetanus is classically considered a complication of wounds. In the present series, 92 persons (54.1 per cent of the group) developed tetanus shortly after a known episode of trauma. Nearly 13 per cent were newborn infants; 11.1 per cent were individuals with chronic ulcerative skin lesions of 2 or more months' duration. Postsurgical tetanus and other cases due to known causes totaled 6 (4.6 per cent). There were 13 persons (7.7 per cent) who had no history or physical

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evidence of injury or open lesions, in whom, therefore, the mode of infection was not apparent. No information was available for 9.4 per cent of the cases (see Table I).

The sex and racial distribution of the patients was similar to that of previous studies in the southeastern United States. Males were stricken more frequently than females, Negroes nearly twice as often as whites (Table II). Individuals under 20 years of age comprised 45.2 per cent of the total. Those aged 21 to 40 accounted for 19.4 per cent of the patients studied. There were 60 persons over 41 years of age (35.2 per cent).

TABLE I. PROBABLE MODE OF TETANUS INFECTION IN DADE COUNTY CASES, 1943 TO 1957

PROBABLE MODE OF INFECTION	TOTAL CASES	CASES FATAL	PERCENTAGE OF CASES DUE TO INDICATED SOURCE
Traumatic	92	47	54.1
Neonatal	22	21	12.9
Chronic skin ulcers	19	11	11.1
Postsurgical	2	1	1.1
Other known causes	6	1	3.5
No known cause	13	5	7.7
No information	16	7	9.4
Total	170	93	99.8%

TETANUS AND CHRONIC SKIN LESIONS

The importance of chronic ulcerative lesions of the skin as the point of entry for tetanus organisms has not been stressed in the literature. Studies in Puerto Rico showed that 13.4 per cent of cases of tetanus among adults were acquired by persons with such ulcers.[2] In Dade County, elimination of neonatal tetanus from the series would make ulcers second to trauma as a source of infection (13.2 per cent).

Of the group of 19 patients who were probably infected through chronic skin lesions, 15 were over 40 years of age. The ulcers had been present from a minimum of 2 months to as long as 20 years at the time of the onset of symptoms. Ulcers which formed after trauma were present in 4 cases for periods ranging from 2 to 8 months before onset of tetanus. Six had stasis or varicose ulcers, some for periods of 2 or 3 years. Two had diabetic ulcers. The cause of the ulcers was not specified in 7 cases described as "chronic." (Table III.)

In all who acquired tetanus through ulcerative breaks in the skin, the lesions were located on the feet, the ankles, or the legs below the knees. In one person, a diabetic, ulcers also were present on the fingers. *Clostridium tetani* was isolated by culture from the ulcer in patient No. 10; organisms morphologically similar to *C. tetani* were found in smears made from the ulcer base in patient No. 3.

TABLE II. AGE, SEX, AND RACE DISTRIBUTION OF ALL TETANUS PATIENTS, DADE COUNTY, 1943 TO 1957

AGE	NEGRO		WHITE		UNKNOWN		TOTAL	
	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES
Neonate	11	6	1	1	2	1	14	8
1–10	19	6	9	5	–	–	28	11
11–20	6	3	5	2	–	–	11	5
21–30	3	6	–	1	–	–	3	7
31–40	9	8	3	3	–	–	12	11
41–50	8	4	1	2	–	–	9	6
51–60	9	3	4	7	1	–	14	10
61–70	6	1	5	1	–	–	11	2
71+	–	1	4	3	–	–	4	4
Subtotal	71	38	32	25	3	1	106	64
Total	109		57		4		170	

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Chronic ulcerative skin lesions present environmental factors favorable for the establishment of tetanus bacilli. The lesions can be infected by wind-borne or dust-borne tetanus spores. Dead and devitalized tissues provide abundant food for a saprophytic organism. Inflammation and impaired circulation, as in

TABLE III. CASES OF TETANUS ARISING IN INDIVIDUALS WITH CHRONIC ULCERATIVE LESIONS OF THE SKIN

PATIENT NUMBER	RACE	AGE	SEX	TYPE OF ULCER	DURATION OF ULCER	SURVIVAL	IMMUNITY STATUS
1	N	60	M	Chronic ulcer of right foot	20 yr.	Died	None
2	N	58	F	Stasis ulcer of leg	2 yr.	Died	None
3*	N	40	M	Posttraumatic leg ulcer	7 mo.	Died	T.A.T. 5 yr. previously
4	N	43	F	Ulcer of leg	9 mo.	Alive	None
5	N	63	M	Posttraumatic	8 mo.	Alive	Unknown
6	N	34	M	Ulcers of legs	6 mo.	Alive	None
7	N	29	F	Varicose leg ulcers	3 yr.	Alive	None
8	W	77	M	Chronic ulcers of feet	"Many years"	Alive	None
9	W	59	F	"Chronic leg ulcers"	Unknown	Died	None
10†	W	64	M	Ulcer of left foot	2 mo.	Died	None
11	N	55	F	Varicose ulcer of right leg	Unknown	Alive	None
12	N	55	M	Ulcer	1 mo.	Alive	None
13	N	47	M	Diabetic ulcers of fingers and toes	Unknown	Died	None
14	W	77	M	Diabetic ulcer of left foot	3 mo.	Died	None
15	W	40	F	Stasis ulcers	"Years"	Died	None
16	W	48	F	Stasis ulcers of left malleolus	Unknown	Died	None
17	N	31	F	Stasis ulcers of ankle	2 yr.	Died	None
18	N	66	M	Posttraumatic ulcer of leg	6 mo.	Died	None
19	W	12	M	Posttraumatic ulcer of ankle	2 mo.	Alive	1 injection of toxoid 1 yr. previously

*Organisms morphologically similar to *Clostridium tetani* seen in smears.

†Culture from ulcer positive for *C. tetani*.

stasis ulcers, diminish tissue oxygenation. Oozing serum, crusting, and the presence of aerophil pyogenic organisms create localized conditions of anaerobiosis essential for the growth of *C. tetani*.

Unlike the situation in which tetanus occurs after trauma, there is no opportunity to offer tetanus antitoxin prophylactically, at or near the time that infection takes place, to the individuals infected via ulcers. In these cases, the onset of symptoms is the first sign that tetanus infection is present. Thus, the only possible way to protect persons with chronic skin breaks is through toxoid immunization, with regular booster injections at least every 3 years to maintain a high level of immunity. Not to do this routinely in patients with chronic ulcerative conditions of the skin in areas where the risk of tetanus infection is high is poor medical practice.

TETANUS AND DIABETES MELLITUS

It is well known that infection is a serious complication of diabetes mellitus; tetanus is not an exception to this rule.

One study has shown the prevalence of diabetes in an American community to be approximately 1.4 per cent of all persons tested. When these results were extended to the individuals not tested, the over-all community rate was calculated as 1.7 per cent.[3] If this latter figure is used, the expected number of diabetics in this series of tetanus cases would be 3 individuals ($0.017 \times 170 = 2.89$). This expected number of diabetics is undoubtedly too high, since the Dade County series contains a larger number of newborn children than would ordinarily be found in a randomly selected sample population of similar size. However, 6 previously known diabetics were found among the tetanus group, more than double the expected number. Furthermore, 2 other persons developing tetanus were found to consistently show glycosuria, and each had fasting blood glucose determinations of more than 150 mg. per cent. Both had familial histories of diabetes mellitus (Table IV).

While this series of cases is too small to draw final conclusions, it appears that more diabetics acquired tetanus than would have been expected on the basis of chance. If the 2 persons who were suspected diabetics are added to the list of diabetics, the disproportionate selectivity of diabetics would be even greater.

The disproportionately high representation of diabetics in this tetanus series cannot be explained simply on the basis that diabetics frequently have ulcerative and gangrenous lesions of the extremities. Two diabetics with tetanus did present such lesions, while in another the onset of tetanus occurred a week following amputation of a foot due to diabetic gangrene. Three diabetics developed tetanus after trauma, 2 after stepping on nails, and 1 after trimming corns with a razor. One person with diabetes who suffered a nail puncture wound received 1,500 units of tetanus antitoxin within 24 hours of injury. In addition, he received daily injections of combined penicillin and streptomycin for 1 week, as well as oral penicillin. The lesion appeared completely healed when the symptoms of tetanus occurred 10 days after the injury.

Of special interest are 2 cases of tetanus which developed in individuals with no known history or physical evidence of trauma and no record of skin ulcers (Table IV). Nearly every series of tetanus cases discussed in the literature has included a group of such persons for whom the site of infection could not be determined. Possibly the diabetics may inoculate themselves with tetanus spores, either through improperly sterilized instruments used for taking insulin or by driving into the tissues spores present on the skin at the site of injection.

TABLE IV. CASES OF TETANUS IN INDIVIDUALS WITH KNOWN DIABETES MELLITUS AND WITH ELEVATED FASTING BLOOD SUGAR

NUMBER	RACE	AGE	SEX	CAUSE OF TETANUS INFECTION	T.A.T	TOXOID	SURVIVAL
Known diabetics							
1	W	55	M	No known injury, no ulcers	None	None	Died
2	N	49	M	No known injury, no ulcers	None	None	Alive
3	W	77	M	Diabetic ulcer, left foot, 3 months' duration	None	None	Died
4	N	47	M	Diabetic ulcers of toes and hands	None	None	Died
5	W	65	M	Stepped on nail	1,500 U.	None	Died
6	N	73	F	Postsurgical (following amputation for diabetic gangrene)	None	None	Died
Patients not diagnosed diabetic, but with fasting blood sugar over 150 mg. per cent							
1*	N	48	F	Stepped on nail	None	Not recorded	Died
2†	N	35	M	Cut corns with a razor	None	None	Died

*Two urine specimens, 4+ glucose; F.B.S., 156 mg. per cent.
†Three urine specimens, 4+ glucose; F.B.S., 250 mg. per cent.

Whatever the reasons for the high incidence of tetanus in diabetics, there is no doubt that the fatality rate for this group is high. Five of the 6 known diabetics who developed tetanus died, as did both persons who were diabetic suspects. This produces case fatality rates of 83.3 per cent for known diabetics and 87.5 per cent for the entire group. These are obviously much higher than the average fatality rates expected in tetanus in adults, which vary in other reports from 35 to 55 per cent. Indeed, one cannot help but wonder if there is some physiologic factor in the diabetic which increases the toxin-producing potential of the tetanus organism or allows better fixation of the neurotoxin to the nerve tissues.

DISCUSSION AND CONCLUSION

Tetanus is a rare disease, comparatively, even in areas with high attack rates. In Dade County the disease affects 2.1 persons per 100,000 population per annum. The majority of cases result from infection of wounds; diabetics and those infected through chronic skin ulcers constitute a minority of those afflicted. Despite its rarity, tetanus carries a high case fatality rate, and the newer drugs and antibiotics have had little effect on changing this situation.

Tetanus toxoid is a means of preventing tetanus or of mitigating the results of acquiring the disease. Unfortunately, tetanus immunization for the entire population seems a goal impossible of achievement except under conditions of military service. Consequently, the problem must be attacked by other means. Immunizing high-risk groups seems one way to accomplish this end; individuals with chronic skin ulcers and those with diabetes mellitus show a special predisposition to this disease. Protecting individuals in these categories routinely through immunization would help decrease the incidence of the disease.

On the basis of the data presented, we consider that tetanus toxoid immunization ought to be given to every person falling into these high-risk groups. This immunization could be administered by giving two injections of tetanus toxoid 1 month apart and a booster dose 1 year after the second injection. Booster doses every 3 years thereafter would maintain high levels of immunity.

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CLINICAL SOCIAL WORK PLANNING WITH 5,000 GENERAL MEDICAL AND SURGICAL PATIENTS FOR THEIR HOSPITAL DISCHARGE

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THE Veterans Administration operates the world's largest system of hospitals, from which approximately 500,000 veterans are discharged annually. Recognized as a leader in the field of medical rehabilitation, the agency seeks to restore each patient to the maximum physical, vocational, psychologic, and social level of which he is capable. In fulfilling this mission it combines the efforts of the physician, dentist, nurse, pharmacist, laboratory technician, psychologist, dietitian, social worker, rehabilitation specialist, etc., into medical teamwork which provides the eligible patient with complete diagnosis, treatment, and rehabilitation.

Eighty-three per cent of the one-half million patients discharged from hospital treatment by the Veterans Administration in 1958 were from the general medical and surgical hospitals. The vast majority of these patients were able to return to their homes, their work, and their normal activities. Many required assistance in dealing with social factors which complicated the medical condition or impeded progress in treatment. Many also required counseling and guidance in adjusting vocational activities to the limitations imposed by illness or disability. With skilled assistance, most of these patients were able to return to the role of head of family and provider expected of this predominately male group.

Of major concern to the Veterans Administration is the increasing number of patients for whom illness or the residual effects of injury necessitate continued nursing or personal care and supervision following hospital discharge. The increasing age of the veteran population is of real significance to the Chief Medical Director and his staff, who have been delegated the responsibility for 125,000 hospital beds for treatment of veterans with service-connected conditions and extension of such treatment to veterans whose disabilities are not of service origin as long as beds are available. There is mounting need for hospital treatment of diseases

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which increase in frequency and severity with aging. When patients move into the hospital for treatment, it is essential that their discharge be expedited as rapidly as inpatient care is completed. The medical team is concerned not only with affording comprehensive medical care, but also with assuring the patient's ability to retain the gains derived from his treatment when he leaves the hospital. To this end, the multi-disciplinary approach to evaluating medical, nursing, and personal care requirements and psychologic and social needs of the patient who cannot be restored to complete self-care is employed. The physician looks to the social worker for skilled appraisal of social and environmental factors which must be considered in the patient's plans for the future and also for the intensive casework necessary to enable the patient to arrive at the plan most suitable for him.

A study conducted by the Central Office Social Work Service in January, 1959, revealed that 1 out of every 20 patients released between Oct. 1 and Dec. 31, 1958, from the 111 general medical and surgical hospitals operated by the Veterans Administration required social work assistance in planning for postrelease care, because of the severity of their illness or the extent of disability.

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Of major significance is the fact that of the 5,065 patients assisted by the social workers in planning for discharge during this 90-day period, 3,399, or 67 per cent, were able to return to their own homes.

RETURN HOME WITH MEDICAL CARE

Of these, 656 (19 per cent) required home-care plans including medical, nursing, and social supervision. In developing these total-care plans, patients were assisted in using personal, family, VA, and community resources, frequently a combination of all.

Example—A 73-year-old, single veteran, with a long history of illness (service-connected—arrested tuberculosis, bronchitis, asthma, old hip fracture; present illness—arteriosclerotic heart disease) was referred to the social worker because "careful planning" was needed in order to insure adequate discharge arrangements. As described by the worker, "although inflexible, he was also sociable and fun-loving and enjoyed contact with other people, especially when he could joke with them." Mr. B. had lived for the past 20 years in a rooming house. There he took all his meals with the family who owned the house, and generally felt very much a part of the family. Because of his long residence there and his feeling of familiarity and security in the home, the patient wanted very much to return, even though this possibility did not seem likely upon initial evaluation. Ambulation was difficult and painful for him, and his room was on the second floor. He needed some supervision in regard to medication, since he was no longer able to remember detailed instructions. He also needed medical supervision and occasionally outpatient care, and his income was limited. His landlady was getting old and had her own health problems, so that she doubted her physical ability to provide the care he required. However, she understood and accepted how important she and her home were to this elderly man. Because of her willingness and the patient's determination, the social worker moved ahead to explore and eventually work out the following arrangements: (1) It was decided that Mr. B. could stay upstairs in his bedroom near the bathroom for the major part of the time. Another roomer, an old-age pensioner, volunteered to bring Mr. B's meals up to him on a regular basis. (2) The landlady's daughter and son-in-law, who lived near, agreed to take a large share of the over-all responsibility for Mr. B. to relieve her and also to do the few monthly business errands Mr. B. required. (3) The landlady agreed to learn, from the visiting nurse, how to check Mr. B's pulse regularly in order to regulate his medication. (4) The visiting nurse agreed to visit every other day initially, to instruct Mr. B.

and to help work out any other unforeseen problems which might arise. Later on, she would decrease her visits to once a week, coming then to check on how things were going and to bathe Mr. B., who jokingly said he had had enough baths at the hospital to last him for 12 years. (5) Mr. B. was referred to the city hospital for outpatient medical care. With the help of the visiting nurse and the landlady's family, Mr. B. would be taken to the clinic at the time he needed his checkups. (6) Mr. B. was discharged on Dec. 18, 1958, but the social worker continued to follow him and work collaboratively with the public nurse in resolving questions and problems which have come up since the discharge. It has been possible for the social worker to evaluate the ongoing adequacy of the placement. Because it has worked out well, continued supervision can soon be terminated.

RETURN HOME WITH FINANCIAL SUPPORT

For the remaining 2,743 patients returning to their homes, needs varied within the wide range of medical and social factors affecting requirements for care and ability of the individual to live with illness or disability. For some patients whose family relationships remained positive and strong, only the more concrete supports were necessary—assurance of adequate income for maintenance and medical care, a visiting or public health nurse to instruct and support the wife in giving personal care until she was sure of herself, more suitable housing, special equipment for the home, etc.

Example.—Mr. E., a 38-year-old married man with two young sons, aged 5 and 11, and a daughter, aged 18, was referred for exploration of discharge resources. Ill with a metastatic carcinoma diagnosed 3 years previously and treated surgically then, the patient now appeared to be going "downhill." The patient wanted very much to return home. The wife accepted his wish, although his nursing care needs were such that she had described herself as "near exhaustion" when the social worker first talked with her at the time of Mr. E's readmission. The social worker gave both support to the wife and tangible help in working out with the public health nurse a plan for instructing the wife about administering narcotics and arranging with the state financial assistance agency for payment for private medical care during the time the patient was at home. With this support and tangible help, Mrs. E. was able to complete plans for the patient's homecoming. Mrs. E's attitude changed from one of realistic reluctance and anxiety, stemming from the multiple problems she initially faced, to one of genuine satisfaction that she had made the decision to work toward her husband's return home.

RETURN HOME WITH SOCIAL CASE WORK

More frequent in the cases reported were situations which required real involvement of the social worker's professional self—e.g., patient or family immobilized by the fear of prolonged illness or disability; ego threatened by reversal of role; lack of understanding obscuring vision into the future; neurotic tendencies intensified, or former channels for handling them appearing to be permanently blocked; positive relationships warped or wavering. In many of these situations the patient's return to the home appeared, on the surface, to be improbable or even impossible.

Example A.—A 50-year-old patient with service-connected bilateral leg amputation, diabetes, and postcerebrovascular accident with left arm paralysis was referred to the social worker by the ward physician for assistance in planning for nursing home care. The patient's wife visited him daily for many weeks, but resisted the doctor's suggestion that she see the social worker. She

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watched closely while the worker interviewed a patient in the next bed and finally consented to talk about her own situation. The social worker encouraged her to discuss her dislike for nursing homes, her fear of inadequacy in caring for the patient at home, and, most of all, her concern about his irritability with her since his operation. The social worker helped her to understand that her husband's attitude was a reaction to his surgical trauma and his subsequent feelings of helplessness after having been a very active person all his life. He also feared being a burden to her. Continued casework with the wife resulted in her decision to try caring for the patient at home. The social worker then helped with the practical aspects of the planning, which included obtaining a hospital bed and sides, visiting nurse service, and an increase in the veteran's pension. A part-time male attendant was secured to assist the wife. Through continued home visits and telephone calls, the social worker helped the wife to maintain confidence in caring for the patient, and she assured the wife of the continued interest of the hospital personnel. Because of the paramount importance in this case of the relationship of the wife to this particular worker, it was decided, for the patient's benefit, to continue helping this woman as the needs arise rather than refer this case elsewhere. Now, 6 months later, the patient is still at home with his wife and doing well.

Example B.—This 35-year-old, unmarried, World War II Army veteran with non-service-connected disability was readmitted to the hospital on July 8, 1958, for a severe form of multiple sclerosis. The ward physician referred the case to the Social Work Service on August 27 for evaluation of a nursing home plan. During the course of hospitalization, the patient benefited considerably from medical and nursing care, including bedside rehabilitation services which increased his self-care activity. Nonetheless, he was severely disabled, was confined to either bed or wheel chair, and required assistance in all major activities of daily living. Fortunately in this case, there was a fairly close-knit family unit. Although the patient recognized that he required considerable nursing care, he did not want to be institutionalized. He preferred returning to his mother, with whom he had lived all his life. While recognizing the problems to be solved—the inadequate housing space in his mother's basement apartment, his mother's employment, some friction with his stepfather, and his own helplessness—he knew he would not be happy among strangers in a nursing home; and he also knew that his sole income of $135.45 a month (Veterans Administration pension plus aid and attendance benefit) would have to be used for nursing home care instead of supplementing the family income where it was needed. The patient's mother was similarly confused about what was best for her son—return home to her, which she realized he wanted, or a nursing home placement. In addition to the practical problems outlined she had to consider her husband's attitude in the matter and assess the extent to which he would be willing not only to have her invalid son at home but to help support them both in the event she stopped work to care for the patient full-time. She required considerable help in working through some distortions about the patient's condition and residual capacities, as well as her ability to deal with day-to-day nursing and psychologic problems.

On the basis of the caseworker's recommendation that nursing home placement was contraindicated and the patient's return to his home feasible, the staff's goal and effort were redirected toward this latter solution. The entire family agreed to the plan of returning the patient to his home and worked through the necessary steps stemming from this joint decision. The worker assisted the family in obtaining public housing, the mother stopped work, the stepfather obtained his employers' permission to live away from the building in which he worked as a superintendent, and the patient worked hard at improving his self-care activities. The patient was discharged on Oct. 7, 1958. Several follow-up telephone calls with the patient's mother since that time have determined that the new arrangement, while demanding on all concerned, is working out satisfactorily. There is no question in the minds of the staff that this patient will eventually require rehospitalization. The worker was, however, able to build upon the positive family relationships to effect the best possible solution for the patient for the present time.

Example C.—Mr. C., a 65-year-old veteran with non-service-connected disability was admitted to the domiciliary section of this center on Aug. 6, 1957, by transfer from another VA hospital. He suffers from parkinsonism and recently required admission to the hospital. He has been confined to a wheel chair for the past 2 months, although he is able to walk for short distances with assistance. He was referred to the Social Service for discharge planning by the ward physician,

since it was felt it would be difficult for him to keep up with the domiciliary routine. In discussing plans for care with Mr. C., he informed the worker that he had recently received a letter from the W. State Hospital informing him that his wife, who had been a patient there for several years, was being considered for possible discharge or furlough. He explained that she was strong and healthy from a physical standpoint and he felt that she would be able to care for him if they could re-establish a home together. The superintendent of the W. State Hospital, when contacted about the feasibility of this plan, stated that Mrs. C. is "in good physical condition and mental adjustment and is able to re-establish a home with Mr. C." The Social Service at the W. State Hospital arranged for Mrs. C. to come to the center by bus. She proved to be a responsible and capable person who was able to complete the necessary details incidental to her husband's discharge with a minimum of assistance. The social worker has made two home visits since discharge, and both Mr. and Mrs. C. seem to be happy and making good adjustments. Mr. C. receives aid and attendance from the VA, as well as Social Security benefits. The total income is slightly over $230.00 monthly, which appears adequate for their needs.

FOSTER HOMES

Thirty-three per cent (1,666) of the patients included in this study group either had no home or required care that could not be given in the home. Plans were developed for 88 of these to go to "foster" homes.

Example A.—Mr. S., a 70-year-old bachelor, veteran of World War I was hospitalized for more than a year for various chronic disabilities largely associated with age, including generalized arteriosclerosis, hypertensive heart disease, prostatic hypertrophy, senile psychoneurosis, and obstipation. He had no home of his own and had lived as a recluse in the same vicinity most of his life. The Social Work Service solicited the help of personnel and volunteers to encourage this man to socialize; this was done at a very slow pace so that he would not feel too threatened, since he was very withdrawn, would never offer conversation, and many times would not reply when spoken to. He gradually responded to a limited extent. When he had made sufficient improvement medically and socially he was approached about discharge planning. He rejected such ideas as domiciliaries, nursing homes, and homes for the aged, but eventually agreed to consider a private family "foster care" home if this could be arranged. A family which had been providing foster care for another veteran agreed to consider taking the patient. Several short visits to this home were arranged for the patient so that he might have coffee with the family and become acquainted. Gradually, the patient accepted the idea of going to this home and a discharge plan was made. This involved education by the social workers of members of the foster family concerning the patient's personality quirks and how to handle them, interviews between the ward physician and foster mother regarding the patient's medical care and diet, and demonstrations by the Nursing Service relative to giving enemas and personal supervision. Following discharge, the social worker made several follow-up visits in the home to help the participants work out adjustment problems. The patient's care is financed from his estate under guardianship. Funds in the estate are from sale of stock and machinery, plus VA non-service-connected disability pension. The patient has made progressive improvement in socializing and physical health. The "foster mother and father" are unusually understanding and are now able to get along with infrequent, self-initiated contacts with the VA social worker.

Example B.—This 78-year-old, widowed veteran of World War I was referred to the Social Work Service by the physician for social evaluation and exploration of planning. Prior to his admission he had been living alone in a furnished room with no cooking facilities. For 3 weeks he had felt too ill to leave his room to get his meals in a nearby restaurant, as was his custom. He did nothing to seek medical attention until a friend requested a physician to make a house call, and hospitalization was recommended. The patient was hospitalized for a calcified abdominal aorta. He was considered by the medical and psychiatric staff as unsuitable for domiciliary care. Nursing home care was not considered desirable since the patient actually did not need nursing care, only supervision. No sound alternative plan was available until a foster home program was established at the hospital. The social worker found that the patient's need for supervision and care and his

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wish to remain in the community could best be met in a foster home, and the patient expressed complete satisfaction with this type of planning. A home was selected in the community where the patient had previously resided for many years. He was able to pay the cost of his care, $130.00 monthly, from his non-service-connected disability pension of $78.75 monthly and his Social Security allowance of $66.50 monthly. The foster mother provided him with a room which he shared with another person, laundry services, and three meals a day served on a tray in his room. The patient preferred to have a casual relationship with the foster mother. In this he would not be expected to react closely. The foster mother met these expectations of the patient, but the patient could not meet the foster mother's expectations in his personal habits, as he was untidy and careless. He was then moved to the home of another foster family in the same community. He expressed some anxiety regarding the move, but the worker was able to help him through his feeling of rejection. The patient is now quite satisfied with this home where he does not experience the pressure to conform to behavior alien to him. He watches television and reads in his room. He feels welcome to participate more actively in the household. He presents no problem to the foster mother, who understands that he lacks the capacity to relate on a closer basis to her and who makes allowances for his untidiness. Continued contact with the home is geared toward maintaining ties with the over-all foster home program in this hospital.

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BOARDING HOMES

One hundred forty-eight of the patients were able to go to established boarding or personal care homes in the community. In most instances there were homes approved or licensed by the public agency authorized by the particular state to enforce legal regulations. In some localities, the social worker had to assume responsibility for determining the proprietor's ability to provide the patient's needs.

Example A.—A 60-year-old man spent 4½ months in this hospital because of residual effects of a stroke. His wife died during that time, and plans for him to return to the community seemed very nebulous at first. In fact, the original referral to Social Work Service from the ward physician mentioned the possibility of transfer to a long-term care service. Exploration of the situation revealed that both physically and financially this patient would be able to manage in a boarding home. With the cooperation of his sister-in-law, a boarding home in his own community was located. This fitted in with patient's own desires for himself and was within his financial means. An only daughter, married, was unable to accept him, but had some plans to take care of him in her home eventually. However, the prospect of the boarding home appealed to the patient and when the proprietor came to the hospital to see him the arrangements were very satisfactorily concluded. This man was thus able to return to his own community, pay for his own accommodations, and be taken care of in an adequate way in consideration of his disability. A premature plan for indefinite institutional care probably would have removed the stimulus from both the patient and relatives for further planning for patient to leave the hospital.

Example B.—Mr. J., an 83-year-old diabetic, Spanish-American War veteran, was referred by the doctor to the Social Work Service for discharge planning. It was believed that his living situation was contributing to his frequent periods of hospitalization. Mr. J., a widower, had been living in a boarding house in a small town. A married son, living in an adjoining state, had given him a home, but the veteran was unhappy there. He said the noise of his small grandchildren irritated him. The other son, single, was unable to offer a home. He was interested in the patient and definitely opposed to his father's returning to his former living arrangement. The patient himself wanted to return to his previous living situation, a boarding house which catered to working men and provided a diet not suitable for the patient. Additional difficulty was the fact that the young men in the boarding home drank and shared their liquor with Mr. J. The landlady herself felt that her home provided a poor environment for him. Before the worker was able to plan with Mr. J., he had first to be helped to accept the fact that he must not return to this former boarding house. When he was able to realize this, he was ready to consider other possibilities. He was

mentally alert, his diabetic condition stabilized with oral medication, and his general condition was good for a man of his age. The patient, his son, and the doctor felt that a boarding home in the vicinity of the hospital which had been used successfully by patients in the past offered the best solution. The social worker explained to the boarding house operator Mr. J's personal problems, his physical condition, and his dietary needs. Since he was a Spanish-American War veteran, his medical needs could be met by our VA Outpatient Service. There was no financial problem since Mr. J. receives a pension and Social Security payments. He is now getting along well physically, enjoys the other members of the home, and is content and satisfied. His son, who lives close enough to visit him conveniently, is pleased with the arrangement and the adjustment which the patient has made.

NURSING HOMES

Approximately 11 per cent (552) of the patients required extensive nursing care or supervision and were assisted in planning for nursing home care. Example A illustrates the borderline situation—the patient who, without comprehensive medical and psychiatric evaluation and the skilled services of the social worker, might well require custodial care in a mental institution. It further shows the capacity of an aged individual, frightened by recognition of damaged mental faculties, to retain mastery of his own life situation, thus sustaining his personal strengths. Other cases show the range of resourcefulness which is brought into play by the social workers in working out plans wherein the severely disabled veteran can receive maximum personal satisfaction together with adequate medical and nursing care.

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Example A.—Mr. A. is a 62-year-old, widowed, World War I veteran who was admitted to the Cardiac Service on Aug. 27, 1958, with arteriosclerotic heart disease with fibrillation. This condition was controlled with medication and considered to be moderate. In addition, Mr. A. has cerebral arteriosclerosis with symptoms of episodic depression, crying spells, inconsistent memory loss, suspiciousness, occasional irrelevant remarks, and a tendency to lose his way and to wander about the hospital. Mr. A's medical problems are considered to be chronic and he will require careful medical and social supervision either at home or in a custodial care institution. Although mentally confused and occasionally disoriented, the patient is considered neither mentally incompetent by the psychiatrist nor in need of commitment to a mental hospital. The family, including several siblings and a married daughter, indicated to the medical staff that they were unable to provide adequate care for the patient at home, and on this basis they were referred to Social Work Service for help in planning.

The patient was initially difficult to involve in a casework relationship. He seemed disinterested in whether he stayed or left the hospital, but readily agreed to the worker's discussing plans for discharge with his daughter. The patient is a retired attorney who had been economically independent and physically self-sufficient until 18 months ago, when he suffered a coronary thrombosis for which he was treated at a private hospital. He had cardiac surgery, from which he made a poor postoperative adjustment and since which he has shown symptoms of senility. The patient has been a widower for 15 years. His only child is the married daughter, who lives with her husband and two children, aged 6 and 8 years. The patient looked to her to solve his problems and would have liked to live in her home. Although warmly related to the patient, the daughter considered this plan unacceptable because the children are fearful of their grandfather and he needs more supervision in the home than she is able to give. The patient has a number of interested siblings. He has lived in several of their homes since his illness and none have been able to manage his behavior or to provide him with the care and watching he needs. (The patient turns on the gas and forgets it, wanders away from home and gets lost, occasionally refuses to wear clothing, worries about the people he "sent to the chair," and expresses fears that he has already died.) The family was so overwhelmed with their inability to plan effectively for the patient that prior

to Social Work Service contact they requested their Congressman to help them have the patient kept in the hospital indefinitely.

The daughter was seen in a series of interviews to help her investigate and evaluate resources for her father's care and to help her recognize and deal with her father's feelings of rejection which were interfering with his willingness to be involved in discharge planning. Interviews with the patient were continued with the goal of trying to minimize some of the fears and anxieties he was experiencing because of his relatively recent sense of physical and mental helplessness. He was able to respond to this approach despite his disturbed behavior in other areas of the hospital. He derived considerable satisfaction in discussing his years as a *bon vivant* and was clearly grieving for the "life that was over for him." He had some insight into his psychiatric problem, in that he recognized his mood swings and considered himself as in the "throes of a mental breakdown." While he could recognize the problem which his psychiatric symptoms presented for others, including his daughter, he shared with the worker his realization that he had little conscious control over his behavior at times and consequently believed that institutional placement might be best for him. Private nursing home facilities were explored and investigated by patient and daughter. A home willing to accept senile patients was found in a community adjoining the daughter's home. Since the cost of $75.00 a week exceeded the patient's income ($100.00 a month from a lawyers' association and $135.45 monthly VA non-service-connected disability pension plus aid and attendance), the family was helped to provide the financial supplementation necessary to implement the plan. The patient left the hospital for the nursing home with a positive attitude, with the hope that he might eventually be well enough to consider more independent plans at a later date.

Example B.—The patient, a 44-year-old, divorced veteran of World War II, was admitted to the hospital in a coma, with a condition subsequently diagnosed as acute encephalopathy, manifested by cerebellar ataxia and expressive aphasia. Approximately 2 months after admission, his condition stabilized to the point where he would shortly attain the maximum hospital benefits possible and become primarily a nursing care problem. Discharge planning was complicated by the fact that patient had no relatives in the community. He desired to return to another state to be near or with his parents. His father and mother, aged 74 and 70 years, respectively, were both receiving old-age assistance and were without other income. Four broad problems were to be considered in planning for the patient's return to his home community: (1) placement upon arrival, (2) money to pay cost of care, (3) transportation back to the home state, and (4) the obvious inability of the patient to transact his own business. Planning involved the Department of Public Welfare in the hometown community, the VA hospital nearest the patient's home, the VA Regional Office Legal and Adjudication Divisions, and the Military Air Force Transport Service. The Department of Public Welfare explored the situation with the parents, interpreting the patient's physical condition and his care requirements. The parents felt that they could not provide the physical care in their own home, but agreed to having the patient in a nursing home where they could visit him regularly. The welfare worker assisted the parents in locating a suitable nursing home where the patient could receive the needed care for $100.00 per month. Non-service-connected disability pension, with aid and attendance allowance, was approved by the Adjudication Division and plans were made by the Legal Division for a guardian. The VA hospital nearest the home accepted transfer via Military Air Force Transport Service for immediate discharge to the parents for nursing home placement. The hospital social worker there saw the parents for confirmation of final details and will provide follow-up supervision for a limited time.

Example C.—Mr. L., 75-year-old bachelor and ex-cowboy, lived alone in a cabin in a small town. Several years ago he fractured his left hip, which resulted in a residual deformity. This has required that he walk with crutches. He has gradually become very deaf. His only living relative, his brother, thought he should have a hearing aid. He bought one but Mr. L. found this difficult to accept, largely because it was his brother's idea. Through the years Mr. L. has maintained several friends, including the County Service Officer, Mr. D. His friend, Mrs. M., who lived in the large house in front of his little shack prepared his meals and helped in caring for him, but she, too, was advanced in years. Mr. L. was admitted to the hospital for a varicose ulcer in the right leg. This slowly healed over a 5-week period, during which time he accepted the idea that he could not return to his one-room home. Mr. D., the Service Officer, took Mr. L. on leave to visit nursing homes in

the area. He decided on one in which there were five other "ex-cowboy" patients and which had a ranch-style screened porch reminiscent of his early cowboy days. His VA pension, plus aid and attendance allowance, meets the cost of care, and the brother can occasionally send additional amounts for medication and medical supervision. The County Service Officer and other friends continue to visit him. Hours are spent recalling "the good old days on the ranch."

SOLDIERS' HOMES

Of this patient group, 368 were determined by the hospital team to be physically and psychologically suitable and able to benefit from care in VA domiciliaries; 152 were accepted for residence in state soldiers' homes; and 358 went to other facilities, including private and parochial homes and institutions for the aged and disabled, as well as state and county homes and hospitals.

TABLE I. DISCHARGE PLANS DEVELOPED FOR 5,065 VA HOSPITAL PATIENTS, SEPT. 1 TO DEC. 31, 1958

TYPE OF CARE	NUMBER OF PATIENTS	PER CENT
Own home	3,399	67
Foster home	88	2
Established boarding or personal care home	148	3
Nursing home	552	11
Veterans Administration domiciliary	368	7
State soldiers' homes	152	3
Private, parochial, county, and state homes and hospitals	358	7
Total	5,065	100

DISCUSSION

All social workers participating in this study considered need for early involvement of the family, where one exists, second only to the patient's own maximum participation in plans for his welfare. They recognized that adequacy or inadequacy of income was the most important factor influencing family attitudes toward assuming responsibility. The positive impact of recent changes in Social Security laws on the total problem of aging and chronic illness has been felt. Veterans receiving dual VA and Social Security benefits can in many geographic areas finance the total cost of chronic care. Public Welfare Departments are now able to meet partial or total costs of medical care in most states. Supervision through visiting or public health nurses is of singular importance to the patient whose home is physically suitable, but whose family needs skilled guidance and instruction in dealing with nursing care problems.

The social workers saw their role as basically that of helping the patient and family to understand and face the reality of the medical situation, as interpreted by the physician, and to mobilize strength and resources to meet the challenge it presents. Many saw their task made lighter by the community's mature approach to coordinated health and social planning. Others saw need for pioneer work in developing social consciousness in the community. All saw participation

in community planning for social and health needs as an essential part of the medical social work job.

SUMMARY

The Social Work Service of the Veterans Administration, on examining one segment of its program, found that 1 out of 20 patients discharged from general medical and surgical hospitals during a 90-day period required assistance with planning for care after release, due to severity of illness or disability.

Table I shows the plans developed for the 5,065 patients.

The major impact of the social worker's activity is shown in the percentage of these patients returning to their own homes. Case examples reflect the involvement in determining, nurturing, and coordinating strength within the patient, family, and community necessary to achieve this record.

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Book Reviews

MOLECULES AND MENTAL HEALTH. Edited by F. A. Gibbs, M.D. Philadelphia, 1959, J. B. Lippincott Co. Pp. 189, not indexed. Price $4.75.

This slim book records the proceedings of two conferences sponsored by the Brain Research Foundation. The first part deals with certain chemicals and their relation to brain function and behavior, and contains mostly old stuff that has received wide attention elsewhere (ceruloplasmin, "taraxein," ergot hallucinogens, tryptophan metabolism in schizophrenics, and acetylcholine effects on behavior). The most interesting material in this section is Elmadjian's data on the excretion and metabolism of epinephrine and norepinephrine in man, and the effects thereon of exertion, excitement, hostility, etc.

The second section deals with a rare epileptic variant seen in pediatric practice and called hypsaryhthmia [*sic*]. It is apparently amenable to ACTH and cortisone treatment (or was considered so in March, 1958).

This book will be of little interest to most physicians, although collectors of typographical errors may enjoy the following from page 14: "Our oxidation curves, like his, were superimpossible." (Or was this a value judgment?)

Louis Lasagna

A SYNOPSIS OF SKIN DISEASES. By Bethel Solomons, Jr., M.A., M.D., F.R.C.P.I. Bristol, 1959, John Wright & Sons Ltd. Pp. 293, indexed. Price $6.75. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents.

This is a small volume which is designed to be an index of dermatology. An attempt is made to sketch the various disorders of the skin with emphasis on etiology, basic descriptive features, differential diagnosis, and therapy. Since it is written in stacatto fashion, a great deal of information is packed into a small size. The reviewer personally approves of this style as one of the basic forms for a textbook. All readers may not agree with the recommended forms of therapy, but most of the facts are well presented. I believe that this book will be useful to many people practicing, teaching, or studying dermatology.

Ernest W. Smith

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